Thyroid, Diabetes and Osteoporosis

The Bermuda Triangle

Livio Luzi
Editor

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The Bermuda Triangle

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Preface

Considering together the overt clinical conditions and the preclinical stages of hypothyroidism, type 2 diabetes mellitus, and osteoporosis, between 50% and 70% of the general population, may have one single disease, or the overlapping of two and three diseases.

In Italy, 10 million people (out of 60 million) have prediabetes or diabetes; approximately 50% of the population (30 million people) have osteopenia or osteoporosis (more women than men are affected), and up to 10% of the population (mainly females) is affected by hypothyroidism (clinical and subclinical). Worldwide, over 537 million adults (20–79 years) were living with diabetes in 2021 (expected to rise to 783 million by 2045). Approximately 500 million people worldwide are estimated to have osteoporosis, with 1 in 3 women and 1 in 5 men over 50 experiencing osteoporotic fractures. The global prevalence of hypothyroidism varies, but estimates suggest around 5% of the population has clinical hypothyroidism, with subclinical cases pushing overall prevalence to 10% or more in many regions.

Although with different pathogenesis, all three conditions induce an increase in morbidity and mortality. All three conditions in different stages of the natural history of the disease may induce accelerated aging and invalidity, causing a dramatic impairment of quality of life.

Among all noncommunicable diseases, thyroid dysfunction, diabetes mellitus, and osteoporosis with their complications (cardiovascular events, cognitive impairment, and fractures) are likely to be the most relevant chronic diseases to determine the increase of Health Organizations costs worldwide.

Whether the three clinical conditions share a common pathogenic pathway is unlikely. Nonetheless, there are many overlapping factors leading to the same potential complications. Firstly, diabetes mellitus and hypo- or hyperthyroid function are common causes of cardiovascular disease. Secondly, hyperthyroid function increases bone fragility. Thirdly, osteoporosis itself is listed today among the complications of type 1 and type 2 diabetes. Lastly, hypothyroidism may increase obesity prevalence and conversely induce type 2 diabetes increment in the general population. All those aspects will undergo an in-depth analysis in the present book.

From all these considerations derives the subtitle of this book: *The Bermuda Triangle*. Like the geographic triangle constituted by Bermuda, Puerto Rico, and Florida, the three clinical conditions may interact in determining life-threatening complications, increasing the overall mortality. Like in the Bermuda Triangle myth, overlapping, confusing, and contrasting clinical pictures may be present, probably related to the preclinical stages of the three diseases (hypothyroid function, prediabetes, osteopenia) which may be as dangerous and as lethal as the related overt diseases, although often asymptomatic and invisible.

A thorough analysis of existing medical evidence as presented herein will help to unravel the real impact of thyroid dysfunction, diabetes, and altered bone metabolism on morbidity and mortality, similarly to what was done in recent years to disprove the Bermuda Triangle myth. No alien entities in the Bermuda were causing the naval and aircraft disasters, but adverse physical and weather conditions. Similarly, strict attention to virtuous life style, the application of precision medicine principles, and a gender-related approach will succeed in understanding, preventing, and treating better thyroid dysfunction, diabetes, and osteoporosis.

Finally, I wish to dedicate this book to the two souls—never friends—of the Endocrinology science, namely, the Diabetologist and the Endocrinologist. In the old days, I began my medical career as a "pure diabetologist" considering the other endocrine diseases secondary—if not boring. In my "physiological academic aging process," I realized that the close interrelationship between diabetes and most other endocrine diseases makes it impossible to treat diabetes without a profound knowledge of all endocrine disease spectrum. Thus, the present work is a mature fruit of my academic career and is mainly dedicated to young professionals working in the area, urging them to span from metabolic to endocrine diseases without close compartmentalization but, in contrast, considering them as a unity. This professional behavior will help them (and their patients) to pass through the Bermuda Triangle unharmed!

Milan, Italy Livio Luzi
July 4th, 2025

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Thyroid, Diabetes, Osteoporosis: Pathophysiology

Thyroid Dysfunction, Metabolic Syndrome, and Cardiovascular Risk

Stefano Massarini and Livio Luzi

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Chapter Introduction: What You Will Learn in This Chapter
This chapter explores the intricate interplay among thyroid dysfunction, metabolic syndrome, and cardiovascular risk. It provides historical insights, epidemiological data, physiological mechanisms, and evidence-based discussion on how thyroid

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hormone imbalances—both overt and subclinical—affect metabolic and cardiovascular health. The chapter also introduces recent findings on the cardioprotective potential of thyroid hormones and their implications for future therapies.

Key Points

- Historical milestones in the understanding and treatment of thyroid dysfunction
- Epidemiology of hypothyroidism, hyperthyroidism, metabolic syndrome, and CVD
- Mechanisms by which thyroid hormones influence cardiovascular physiology
- Clinical impact of subclinical and overt thyroid dysfunctions on cardiovascular outcomes
- Emerging evidence on thyroid hormone therapy for cardioprotection

Learning Objectives

By the end of this chapter, readers will be able to:

- Describe the epidemiological burden of thyroid dysfunction and metabolic syndrome.
- Explain the physiological roles of thyroid hormones in cardiovascular health.
- Distinguish between overt and subclinical thyroid disorders and their cardiovascular implications.
- Discuss the current evidence and guidelines regarding treatment of thyroid dysfunctions.
- Evaluate emerging research on thyroid hormone-based cardioprotection.

Definitions

- *Thyroid Hormones (THs)*: Hormones secreted by the thyroid gland, primarily thyroxine (T4) and triiodothyronine (T3), which regulate metabolism and influence cardiovascular function.
- *Hypothyroidism*: A clinical condition characterized by insufficient production of thyroid hormones.
- *Hyperthyroidism*: A condition marked by excessive production of thyroid hormones.
- *Subclinical Thyroid Dysfunction*: Abnormal TSH levels with normal circulating thyroid hormones, often asymptomatic but potentially significant.
- *Metabolic Syndrome*: A cluster of metabolic risk factors (e.g., central obesity, hypertension, dyslipidemia, insulin resistance) that increase the risk of CVD and T2DM.
- *Cardioprotection*: Strategies aimed at preserving cardiac function and reducing myocardial injury following ischemic events.

1 History

The clinical syndrome now recognized as hypothyroidism was first described as myxedema in 1878 by William Ord, a physician at St. Thomas' Hospital [1].

The history of thyroid hormone therapy began in 1891, when George Murray, an English physician, administered subcutaneous injections of sheep thyroid extract to a 46-year-old woman exhibiting classic signs and symptoms of myxedema [2]. Remarkably, the patient maintained excellent health until 1919, eventually passing away from cardiac failure at age 74. This case demonstrated the effectiveness of continuous thyroid extract therapy, allowing the patient to live more than 28 years in good health after a diagnosis of advanced myxedema.

Murray's findings supported several important conclusions: (1) The thyroid is purely an internal secretory gland. (2) Myxedema symptoms can be completely reversed through continuous administration of thyroid extract. (3) Thyroid function in humans can be sustained indefinitely by substitutive therapy with animal-derived hormones. (4) Life expectancy need not be reduced by thyroid atrophy if substitution therapy is maintained appropriately [3].

In December 1914, Edward Kendall, PhD, at the Mayo Clinic, isolated thyroid hormone crystals and named the compound thyroxin [4–6]. A decade later, Charles Harington and George Barger determined the chemical structure and synthesized thyroxine in 1926 and 1927, respectively [7, 8]. These discoveries highlighted the significance of iodine as a fundamental component of tetraiodothyronine (T4).

In 1931, D.M. Lyon was the first to demonstrate a relationship between thyroid function and obesity, specifically implicating lymphoid tissue [9]. In the early 1950s, Gross and Pitt-Rivers reported the biological activity of triiodothyronine (T3) [10].

Further advances in thyroid physiology came in 1931, when Loeb and Bassett extracted and purified thyrotropic hormone (TSH) from bovine pituitary glands [11]. In 1949, R.G. Hoskins elaborated the functional concept of the pituitary-thyroid axis [12], and in 1970, Andrew Schally and Roger Guillemin isolated thyrotropin-releasing hormone (TRH), thus defining the hypothalamic-pituitary-thyroid axis [13, 14].

Until 1971, desiccated thyroid extract remained the most commonly used treatment for myxedema, primarily due to its low cost [15]. However, by 1978, oral sodium L-thyroxine began replacing desiccated thyroid in clinical practice [16]. In 1989, levothyroxine was recognized as the drug of choice for hypothyroidism management [17], and by 1996, it became preferred due to its long half-life, ease of absorption, accurate dosing, and wide availability in multiple strengths [18].

In 2012, the American Thyroid Association (ATA) recommended L-thyroxine monotherapy, stating that there was no evidence supporting the use of synthetic combination therapies and advising against the use of desiccated thyroid hormone [19]. In 2014, the ATA reaffirmed levothyroxine as the first-line treatment for hypothyroidism due to its proven efficacy, favorable safety profile, convenient administration, reliable intestinal absorption, long serum half-life, and affordability [20].

Levothyroxine replacement therapy today is guided by three primary goals: (1) To resolve symptoms and clinical signs of hypothyroidism, including physiological and biochemical abnormalities, (2) to normalize serum TSH and improve thyroid hormone levels, and (3) to avoid overtreatment, particularly in elderly patients, in order to prevent iatrogenic thyrotoxicosis [20].

2 Epidemiology

Cardiovascular disease (CVD) remains the leading cause of death worldwide. According to the Global Burden of Disease (GBD) study, approximately 17.8 million deaths from CVD occurred globally in 2017, marking a 21% increase over the preceding decade. Ischemic heart disease (IHD) and stroke were responsible for nearly 50% and 35% of these deaths, respectively [21]. Despite this increase in absolute numbers, age-standardized death rates for CVD declined by approximately 10% over the same period [21].

In Europe, significant declines in age-standardized mortality rates from CVD [22–30], IHD [31], and stroke [32] have been observed since the early 1980s. Nevertheless, CVD remains the most common cause of death across the continent [25, 27, 28]. It is estimated that CVD causes nearly 4 million deaths annually in Europe, accounting for approximately 44% of all deaths. Among these, IHD represents 44% and stroke 25% of CVD-related mortality [24, 25, 28, 29, 31].

According to Townsend et al., CVD is responsible for over 3.8 million deaths per year in Europe—approximately 1.76 million in men and more than 2 million in women. This translates to 39% of all male deaths and 46% of all female deaths. In most countries, the median percentage of deaths attributable to CVD is higher in women (47%) than in men (38%). IHD is the leading cause of CVD deaths in both sexes, accounting for 47% of deaths in men and 40% in women. Interestingly, a similar number of men (n = 819,104) and women (n = 813,191) died from IHD, whereas more than 500,000 women and fewer than 400,000 men died from stroke [22].

Hypothyroidism is also a common condition globally. The primary causes of hypothyroidism include iodine deficiency and autoimmune thyroid disease [33, 34]. Approximately 33% of the world's population lives in iodine-deficient regions, and the consequences of severe iodine deficiency—especially on the neurological development of fetuses and children—are well-documented [35].

In iodine-sufficient countries, the prevalence of hypothyroidism ranges between 1% and 2% in the general population [36, 37], with rates increasing to 7% among individuals aged 85–89 years [38]. Hypothyroidism is about ten times more prevalent in women than in men [36]. In Europe, the prevalence of overt hypothyroidism ranges from 0.2% to 5.3% [39, 40], while in the United States, it ranges from 0.3% to 3.7% [41].

According to the Centers for Disease Control and Prevention (CDC), the prevalence of metabolic syndrome in the United States increased by 35% between the

1980s and 2012 [42]. The metabolic syndrome often overlaps with type 2 diabetes mellitus (T2DM); approximately 85% of individuals with T2DM also meet the criteria for metabolic syndrome, substantially increasing their risk of CVD [43].

In 2017, about 12.2% of the US adult population had T2DM, with nearly 25% of these individuals being unaware of their diagnosis. Notably, the prevalence of metabolic syndrome was nearly three times higher, affecting approximately one-third of US adults [44, 45]. However, recent data from the National Health and Nutrition Examination Survey (NHANES) suggest a decline, with metabolic syndrome affecting 24% of men and 22% of women [46, 47].

3 Thyroid Hormones and Cardiovascular Disease

Thyroid hormones (THs) play a pivotal role in regulating metabolic processes critical for normal growth and development, as well as maintaining metabolic homeostasis in adulthood [48]. TH status is closely linked to body weight and energy expenditure [49]. In states of hyperthyroidism, characterized by an excess of circulating thyroid hormones, a hypermetabolic state occurs, which includes increased resting energy expenditure, weight loss, reduced serum cholesterol levels, enhanced lipolysis, and upregulated gluconeogenesis [50, 51]. Conversely, hypothyroidism, marked by a deficiency of thyroid hormones, results in hypometabolism, with reduced energy expenditure, weight gain, increased cholesterol levels, diminished lipolysis, and impaired gluconeogenesis [52]. Although TH stimulates both lipogenesis and lipolysis, the net effect at elevated levels is a reduction in fat mass [53].

Most circulating triiodothyronine (T3) is generated through the extrathyroidal deiodination of thyroxine (T4), a process mediated by deiodinase enzymes. These enzymes, therefore, play a crucial role in regulating tissue-specific TH activity.

Thyroid hormones exert multiple effects on the cardiovascular system, particularly on the heart, through three principal mechanisms: by direct genomic actions via nuclear TH receptors in cardiomyocytes, regulating the expression of genes critical to myocardial function; by extranuclear, nongenomic actions through modulation of membrane ion channels in cardiomyocytes; and Peripheral hemodynamic effects: by altering systemic vascular resistance, cardiac preload, and contractility [54, 55].

In cardiomyocytes, the relevant deiodinases include type II iodothyronine deiodinase (DIO2), which activates TH by converting T4 to T3, and type III deiodinase (DIO3), which inactivates both T4 and T3, thereby terminating TH action.

Thyroid hormones exhibit positive inotropic and chronotropic effects, enhancing both myocardial contractility and heart rate [56].

These actions are mediated through the transcriptional regulation of key cardiac proteins. Specifically, TH: upregulates the expression of Na^+/K^+-ATPase, myosin heavy chain-α (MYH6), and sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2); downregulates the expression of myosin heavy chain-β (MYH7) and phospholamban (PLN) [57–59].

The SERCA2/PLN system is crucial for calcium handling in the sarcoplasmic reticulum. SERCA2 promotes calcium reuptake during diastole, and PLN acts as its inhibitor. TH enhances cardiac relaxation and diastolic function by increasing SERCA2 and suppressing PLN expression, thereby facilitating more efficient ventricular relaxation [60, 61].

In addition to genomic mechanisms, THs exert nongenomic effects by modulating: ion channel activity (sodium, potassium, and calcium channels); mitochondrial biogenesis; and intracellular signaling pathways that influence myocardial energy metabolism and contractility [62, 63].

These rapid, nontranscriptional effects complement the genomic regulation and are essential for the fine-tuning of cardiac performance under varying physiological conditions.

3.1 Overt and Subclinical Hyperthyroidism

Hyperthyroidism is a common thyroid disorder. The term hyperthyroidism defines a syndrome associated with excess thyroid hormone production.

Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is defined as low or suppressed thyroid-stimulating hormone (TSH) levels with elevated triiodothyronine (T3) levels and/or elevated thyroxine (T4) levels. Subclinical hyperthyroidism is characterized by low or suppressed TSH with normal T3 and T4 levels. Both overt and subclinical hyperthyroidism affect the cardiovascular system.

The most common causes of excessive thyroid hormone production are Graves' disease, toxic multinodular goiter, and toxic adenoma. The most common cause of excessive passive release of thyroid hormones is painless (silent) thyroiditis, although its clinical presentation is the same as other causes.

In the United States, the overall prevalence of hyperthyroidism is 1.2%, with prevalences of overt hyperthyroidism and subclinical hyperthyroidism being 0.5% and 0.7%, respectively [64].

Tachycardia is a common sign of overt hyperthyroidism, and 5–15% of patients with overt hyperthyroidism present with atrial fibrillation (AF) [54].

Nakazawa et al. demonstrated that spontaneous reversion of atrial fibrillation to sinus rhythm in 60% of patients who have AF due to hyperthyroidism is highly unlikely if the duration of atrial fibrillation before achieving a euthyroid state exceeds 13 months, or if it is still present after the patient has been euthyroid for 4 months [65].

Subclinical hyperthyroidism can be caused by exogenous or endogenous factors.

The prevalence of endogenous subclinical hyperthyroidism in the general population depends on age, sex, and iodine intake, with a reported prevalence of 0.6–1.8% in iodine-sufficient areas in Iceland and the United States, and as high as 9.8% in iodine-deficient areas in Denmark [66, 67].

However, although exogenous and endogenous subclinical hyperthyroidism are equivalent in terms of cardiovascular effects, the association between subclinical hyperthyroidism and cardiovascular outcomes remains conflicting [56].

In large, population-cohort study of 3300 older individuals (aged >50–70 years), the Echocardiographic left ventricular mass divided by height(2·7) (LVMI(ht)), and LVH(ht) (LVMI(ht) > 44 g/m(2·7) in women and >48 g/m(2·7) in men) was measured at baseline and after 5-year follow-up (median 5·00; range 4·92; 5·08). At follow-up, left ventricular hypertrophy LVMI(ht) did not differ between subjects with and without Scheme (50·2 g/m(2·7), interquartile range (IQR) 41·2; 59·5 vs. 47·8 g/m(2·7), IQR 39·3; 56·9; $P = 0·29$). LVH(ht) was present in 66 (61·7%) subjects with and 543 (54·0%) persons without Scheme ($P = 0·13$). Analyses revealed no association between SCH and progression of LVMI(ht) ($\beta = -0·18$; 95%-confidence interval (CI) -2·34; −1·99; $P = 0·873$), and development of LVH(ht) (relative risk 0·86, 95%-CI 0·60; 1·26; $P = 0·462$), respectively. Therefore, subclinical hyperthyroidism had no impact on progression of LVMI and development of LVH during 5-year follow-up in subjects aged 45 years or older [68].

A patient-level meta-analysis of 10 prospective cohort studies, including a total of 52,674 participants, demonstrated that endogenous subclinical hyperthyroidism is associated with increased risks of total mortality, coronary heart disease (CHD) mortality, and incident AF, with the highest risks of CHD mortality and AF when the thyrotropin level is lower than 0.10 mIU/L. Specifically, in age- and sex-adjusted analyses, subclinical hyperthyroidism was associated with increased total mortality (hazard ratio [HR] 1.24, 95% CI 1.06–1.46), CHD mortality (HR 1.29; 95% CI 1.02–1.62), CHD events (HR 1.21; 95% CI 0.99–1.46), and AF (HR 1.68; 95% CI 1.16–2.43). Risks did not differ significantly by age, sex, or preexisting cardiovascular disease and were similar after further adjustment for cardiovascular risk factors, with attributable risks ranging from 14.5% for total mortality to 41.5% for AF in those with subclinical hyperthyroidism. Risks for CHD mortality and AF (but not other outcomes) were higher for a thyrotropin level < 0.10 mIU/L compared with 0.10–0.44 mIU/L (for both, P for trend = 0.03) [69].

The European Thyroid Association guidelines advocate treatment in patients aged >65 years with TSH levels <0.10 mU/L to reduce the risk of cardiovascular events, fractures, or progression to overt hyperthyroidism [70].

Treatment can also be considered in patients aged >65 years with mildly low TSH levels (0.10–0.39 mU/L), particularly if they have underlying cardiovascular disease or other comorbidities [70].

In patients aged <65 years with TSH levels <0.10 mU/L, treatment is indicated in those with cardiovascular risk factors or comorbidities, persistent thyroid disease, and/or symptoms of thyroid disease, especially if thyroid autoantibodies are present [70].

Finally, the task force concluded that there are no data to support treating subclinical hyperthyroidism in younger asymptomatic patients with grade 1 subclinical hyperthyroidism. These patients should be monitored without treatment due to the low risk of progression to overt hyperthyroidism and the weaker evidence for adverse health outcomes [70].

3.2 Overt and Subclinical Hypothyroidism

Hypothyroidism results from low levels of thyroid hormone with varied etiology and manifestations. Untreated hypothyroidism increases morbidity and mortality. In the United States, autoimmune thyroid disease (Hashimoto thyroiditis) is the most common cause of hypothyroidism, but globally, lack of iodine in the diet is the most common cause. The prevalence of overt hypothyroidism in nonpregnant adults is 0.2–2.0% [41, 71].

The NHANESIII (National Health and Nutrition Examination Survey) study found the prevalence of overt hypothyroidism among adults in the United States (12 years of age and older) to be 0.3% and subclinical hypothyroidism 4.3%. Female gender and increasing age were associated with higher thyroid-stimulating hormone (TSH) and the prevalence of antithyroid antibodies [72].

Hypothyroidism is more prevalent in women with small stature at birth and low body mass index in childhood.

The patient presentation can vary from asymptomatic disease to myxedema coma. Today, the diagnosis of hypothyroidism is easily made with simple blood tests and can be treated with exogenous thyroid hormone.

Hypothyroidism is majorly divided into two categories: primary and secondary (central) hypothyroidism. Hypothyroidism is termed primary when the thyroid gland itself is not able to produce adequate amounts of thyroid hormone. The less common, secondary, or central hypothyroidism is labeled when the thyroid gland itself is normal, and the pathology is related to the pituitary gland or hypothalamus.

The most prevalent etiology of primary hypothyroidism is iodine deficiency in iodine-deficient geographic areas worldwide. Autoimmune thyroid diseases are the leading causes of hypothyroidism in the United States and iodine-sufficient regions. Hashimoto thyroiditis is the most common etiology in the United States, and it has a strong association with lymphoma. Etiology can be influenced locally by iodine fortification and the emergence of new iodine-deficient areas [34].

Other common causes of hypothyroidism include drugs such as amiodarone, thalidomide, oral tyrosine kinase inhibitors (sunitinib, imatinib), stavudine, interferon, bexarotene, perchlorate, rifampin, ethionamide, phenobarbital, phenytoin, carbamazepine, interleukin-2, and lithium, thyroid radioactive iodine therapy, thyroid surgery, radiotherapy to head or neck area, central hypothyroidism from neoplastic, infiltrative, inflammatory, genetic, or iatrogenic disorders of the pituitary or hypothalamus [19].

Postpartum thyroiditis affects nearly 10% of women and often presents 8–20 weeks after the delivery of the infant. Only a few women require treatment with thyroid hormone. However, some women are at high risk for permanent hypothyroidism or recurrent postpartum thyroiditis in future pregnancies [73].

The use of radioactive iodine to manage Graves' disease usually results in permanent hypothyroidism in about 80–90% of the patients within 8–20 weeks after treatment. Radiation treatment to the head and neck area can also result in hypothyroidism [73].

Overt hypothyroidism has several cardiac manifestations, including a reduction in cardiac output and cardiac contractility, a decrease in heart rate, and an increase in peripheral vascular resistance [74].

Cappola and Ladenson showed that the growing understanding of thyroid hormone's regulation of lipid and homocysteine metabolism, effects on vascular reactivity and blood pressure, and modulation of other atherosclerotic factors now provide partial explanations for how hypothyroidism predisposes patients to cardiovascular disease. In addition to this pathogenic relationship, the multiple direct and indirect actions of thyroid hormone on cardiac and peripheral vascular functions can complicate the management of hypothyroid patients with atherosclerotic coronary disease [75]. All these clinical features are reversible with thyroid hormone replacement therapy.

Regarding subclinical hypothyroidism, the most frequent cardiac abnormality is diastolic dysfunction owing to impaired ventricular filling and relaxation [76, 77].

A study by Ripoli et al. in 2005 analyzed the thyroid profile on cardiac volumes and function in 30 females with subclinical hypothyroidism and 20 matched control subjects. Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV), stroke volume (SV), cardiac index (CI), and systemic vascular resistance (SVR) were calculated by cardiac magnetic resonance (CMR). This study demonstrated that subclinical hypothyroidism was associated with systolic dysfunction that reversed with thyroxine replacement therapy [78].

Findings from meta-analyses of observational studies suggest that subclinical hypothyroidism is associated with increased ischemic heart disease (both prevalence and incidence) and cardiovascular mortality only in subjects from younger populations. These data suggest that increased vascular risk may only be present in younger individuals with subclinical hypothyroidism [79].

A meta-analysis of individual data on 55,287 participants with 542,494 person-years of follow-up between 1972 and 2007 was supplied from 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan. The risk of CHD events was examined in 25,977 participants from 7 cohorts with available data. Among 55,287 adults, 3450 had subclinical hypothyroidism (6.2%) and 51,837 had euthyroidism. In age- and sex-adjusted analyses, the hazard ratio (HR) for CHD events was 1.00 (95% confidence interval [CI], 0.86–1.18) for a TSH level of 4.5 to 6.9 mIU/L (20.3 vs 20.3/1000 person-years for participants with euthyroidism), 1.17 (95% CI, 0.96–1.43) for a TSH level of 7.0 to 9.9 mIU/L (23.8/1000 person-years), and 1.89 (95% CI, 1.28–2.80) for a TSH level of 10–19.9 mIU/L (n = 70 events/235; 38.4/1000 person-years; $P < 0.001$ for trend). The corresponding HRs for CHD mortality were 1.09 (95% CI, 0.91–1.30; 5.3 vs 4.9/1000 person-years for participants with euthyroidism), 1.42 (95% CI, 1.03–1.95; 6.9/1000 person-years), and 1.58 (95% CI, 1.10–2.27, n = 28 deaths/333; 7.7/1000 person-years; $P = 0.005$ for trend). Total mortality was not increased among participants with subclinical hypothyroidism. Results were similar after further adjustment for traditional cardiovascular risk factors. Risks did not significantly differ by age, sex, or preexisting cardiovascular disease. Hence, subclinical hypothyroidism is associated with an

increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater [80].

Owing to the lack of evidence from prospective, randomized, controlled trials in subclinical hypothyroidism, international guidelines indicate that treatment should be considered only in those individuals with severe disease (serum TSH >10 mU/l), with symptoms of hypothyroidism, or in individuals aged <70 years, particularly if they also have other cardiovascular risk factors [81].

3.3 Cardioprotection and Thyroid Hormones

Following myocardial infarction (MI), cardioprotection has emerged as a key therapeutic target in both the acute and chronic phases, aiming to limit infarct size and prevent the progression to heart failure. Cardioprotection is a multifactorial process involving cell growth stimulation, neoangiogenesis, metabolic adaptation, and, increasingly recognized, the preservation of mitochondrial integrity [82].

The thyroid system is tightly interconnected with cardiac homeostasis, and recent studies have highlighted the cardioprotective role of thyroid hormones (THs), particularly through the maintenance of mitochondrial structure and function, antifibrotic and proangiogenic effects, and the potential to induce cell regeneration and growth [82].

Several experimental studies in rodent models of acute MI have shown that treatment with triiodothyronine (T3) limits infarct expansion by reducing myocyte apoptosis. This occurs through the activation of prosurvival signaling pathways such as PI3K/AKT and protein kinase C, and the inhibition of proapoptotic pathways like p38 MAPK [83–86]. These findings suggest that THs exert direct antiapoptotic effects at the myocardial level.

Interestingly, thyroid hormones exhibit a dose-dependent biphasic effect on postischemic cardiac function, potentially mediated by differential activation patterns of intracellular signaling pathways such as Akt and ERK [87].

Mitochondrial dysfunction is a key contributor to cardiomyocyte death during ischemia/reperfusion (I/R) injury. Under these conditions, the tumor suppressor p53 is activated and initiates several pathways detrimental to mitochondrial function. p53 is negatively regulated by miR-30, whose expression decreases during ischemia. Forini et al. demonstrated that T3 administration post-MI enhances cardiac recovery, partially by restoring miR-30a levels in the area at risk (AAR), leading to p53 mRNA downregulation. This molecular cascade results in reduced Bax expression, stabilization of mitochondrial membrane potential, and decreased apoptosis and necrosis. In primary neonatal rat cardiomyocytes, T3 also prevented hypoxia-induced miR-30a suppression and p53 upregulation. The cardioprotective effect of T3 was significantly diminished when miR-30a was silenced, suggesting that the miR-30a/p53 axis is a crucial mediator of T3-induced mitochondrial protection [88].

Further evidence from a 2013 study indicated that long-term thyroxine (T4) treatment following MI promoted favorable remodeling of myocytes, arterioles, and extracellular matrix in noninfarcted regions, and improved survival of myocytes in the peri-infarct zone [89].

In animal models, low-dose oral T3 has been shown to markedly enhance post-MI cardiac performance, reduce atrial arrhythmias and pathological remodeling, and reverse adverse gene expression changes, without evident toxicity. These findings support the potential for clinical translation of this approach [90].

Altogether, both observational clinical data and robust experimental evidence suggest that alterations in thyroid hormone signaling negatively impact cardiac structure and function, while appropriate thyroid hormone supplementation may offer therapeutic cardioprotective benefits [56, 85, 91, 92]. Nevertheless, confirmation from well-designed randomized controlled trials is needed to assess the efficacy and safety of thyroid-hormone-based therapies in postischemic cardiac settings.

Future studies are needed to clarify the optimal timing, dosage, and formulation of thyroid hormone therapy in patients with cardiovascular diseases, particularly in the postmyocardial infarction setting. In addition, research should investigate the potential of thyroid hormones or thyroid-targeted therapies as adjunctive treatments aimed at enhancing cardiac repair and preventing adverse remodeling. Advances in molecular cardiology, including the study of miRNAs and mitochondrial pathways, offer promising avenues to uncover new mechanisms of thyroid-mediated cardioprotection. These perspectives may pave the way toward more personalized and endocrine-guided strategies for cardiovascular disease prevention and management.

Questions for Self-Assessment

1. *What is a common cardiovascular manifestation of overt hypothyroidism?*

   (a) Increased heart rate and decreased peripheral resistance
   (b) Reduced cardiac output and increased peripheral resistance
   (c) Enhanced myocardial contractility and increased cardiac output
   (d) Increased risk of ventricular fibrillation in young adults

   Correct answer: (b) Reduced cardiac output and increased peripheral resistance

2. *How does subclinical thyroid dysfunction differ from overt thyroid disease?*

   (a) Subclinical dysfunction shows abnormal TSH and abnormal T3/T4 levels.
   (b) Subclinical dysfunction is more common in men and presents with overt symptoms.
   (c) Subclinical dysfunction has abnormal TSH but normal T3 and T4 levels, often asymptomatic.
   (d) Subclinical dysfunction cannot be detected through laboratory tests.

   Correct answer: (c) Subclinical dysfunction has abnormal TSH but normal T3 and T4 levels, often asymptomatic.

3. *Which of the following is not considered a typical component of metabolic syndrome?*

   (a) Abdominal obesity
   (b) Hypertension
   (c) Hyperthyroidism
   (d) Insulin resistance

   Correct answer: (c) Hyperthyroidism

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Diabetes, Thyroid, and Bone Fragility: A Dangerous Triangle

Carmine Gazzaruso and Adriana Coppola

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Chapter Introduction: What You Will Learn in This Chapter
In this chapter, we explore the complex and multifaceted relationship among diabetes, thyroid dysfunction, and bone fragility. These three conditions are interconnected, often exacerbating each other, leading to an increased risk of fractures and other skeletal problems in affected patients. The chapter focuses on understanding the underlying physiological and metabolic mechanisms that link these three systems, with particular emphasis on how thyroid disorders influence bone health in diabetic patients. We will also delve into the diagnostic challenges and therapeutic approaches necessary to address bone fragility in the context of diabetes and thyroid dysfunction.

Key Points
- The physiological mechanisms of bone metabolism and the impact of thyroid hormones on bone health

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- How diabetes, both type 1 and type 2, interacts with thyroid dysfunction to accelerate bone loss
- The pathophysiological mechanisms linking thyroid disorders and bone fragility, including changes in bone turnover, microarchitecture, and the role of osteocytes
- The impact of diabetes medications on bone health and fracture risk
- Current therapeutic strategies to prevent and manage bone fragility in patients with diabetes and thyroid dysfunction

By the end of this chapter, readers will gain a deeper understanding of the interplay among diabetes, thyroid dysfunction, and bone fragility, which will inform clinical decision-making for managing these complex patients.

Learning Objectives

Upon completing this chapter, readers should be able to:

- Understand the biological mechanisms linking thyroid disorders, diabetes, and bone fragility.
- Identify the role of thyroid hormones in bone metabolism and how this is altered in diabetes.
- Recognize the impact of thyroid dysfunction on bone density and the risk of fractures in diabetic patients.
- Describe the pathophysiological mechanisms leading to bone fragility in the context of diabetes and thyroid dysfunction.
- Evaluate the therapeutic strategies for managing bone health in patients with both thyroid and metabolic disorders.

Definitions

- *Thyroid Dysfunction*: Refers to abnormal thyroid function, which includes both hypothyroidism (underactive thyroid) and hyperthyroidism (overactive thyroid). These conditions impact various metabolic processes, including bone metabolism.
- *Diabetes*: A chronic metabolic disorder characterized by high blood glucose levels resulting from either insufficient insulin production (type 1 diabetes) or insulin resistance (type 2 diabetes). Diabetes can affect multiple organs, including the bones.
- *Bone Fragility*: A condition characterized by decreased bone strength and an increased risk of fractures. It is commonly observed in patients with diabetes and thyroid disorders due to alterations in bone turnover and quality.
- *Osteocytes*: Bone cells embedded within the bone matrix that play a critical role in maintaining bone homeostasis. Dysfunction or senescence of osteocytes is a key factor in bone fragility in both thyroid disorders and diabetes.
- *Advanced Glycation End-products (AGEs)*: Molecules formed when glucose reacts with proteins or lipids. AGEs accumulate in various tissues, including bone, and contribute to bone stiffness and fragility, particularly in diabetic patients.

1 Osteoporosis and Bone Fragility: New Insights and New Concepts

Osteoporosis is a systemic bone disease characterized by a reduction in bone strength and an increased risk of fractures [1, 2]. In the past, osteoporosis has been clinically based primarily on bone quantity, usually measured by bone mineral density (BMD) using techniques such as dual-energy X-ray absorptiometry (DXA) [1, 2]. Low BMD was considered the main feature of osteoporosis, and prevention strategies were almost exclusively directed at preserving or increasing bone mass [3]. However, this initial conceptual model was insufficient to explain an individual's true fracture risk, as many patients with only moderately low BMD still developed fragility fractures, while others with low BMD remained fracture-free. This difference served as a basis for the construction of the concept of osteoporosis, moving from an interest in bone quantity to a better understanding of bone quality as an important determinant of bone strength, bone stiffness, and fracture risk [3, 4].

Bone quality encompasses a set of structural and material properties that influence its mechanical efficiency. These include properties such as microarchitecture, turnover, degree of mineralization, collagen quality, and microscopic damage accumulation [1]. Trabecular bone, which is mainly involved in the structural support of vertebrae and end segments of long bones, becomes thinner, disconnected, and shows greater heterogeneity in brittle bone [3, 4]. Cortical bone, which is extremely important for the mechanical strength of the skeleton, also becomes progressively more porous and less dense. Together, these structural defects compromise the mechanical properties of the bone, reducing its ability to withstand even low-energy trauma [1].

At the material level, brittleness is determined by alterations in the organic matrix and minerals. Mineral crystals are abnormally large and disordered, compromising their deformation resistance role [5]. Alterations in collagen cross-linking can lead to increased fragility of bone, reducing its toughness and energy absorption capacity [3, 4].

Bone remodeling is a continuous and dynamic process necessary to preserve the integrity of the skeleton throughout an individual's lifetime. It involves the concerted activities of osteoclasts, which resorb old or damaged bone, and osteoblasts, which deposit new bone tissue. This tightly controlled cycle replaces microdamaged bone with new mechanically competent tissue, preserving bone strength and mineral homeostasis [1]. Bone remodeling occurs in discrete packets called basic multicellular units and is controlled by mechanical loads, hormonal stimuli, and local cytokines.

Disruption of bone remodeling mechanisms is at the root: excessive bone resorption or insufficient bone formation can weaken the skeleton. Increased bone turnover, typically associated with increased resorption, can make bone undermineralized and vulnerable to microdamage, while low turnover states can allow the formation of unrepaired microfractures, both of which eventually lead to structural weakness [1].

In summary, the definition and meaning of osteoporosis have expanded considerably in recent decades. The disease is currently identified as a disorder of loss of bone strength due to defects in bone quantity and quality. Brittle bones are not only less dense but are structurally defective and materially weaker and thus more prone to fracture. It is necessary to respect this complexity in order to make a correct diagnosis, estimate the risk, and successfully treat osteoporosis in a way that seeks to preserve both the mass and the innate quality of the skeletal system.

2 Methods for Assessing Bone Quantity and Quality

Recent advances in bone health research have developed new strategies to assess skeletal fragility in addition to the traditional assessment of BMD. Although BMD measured by DXA remains the gold standard for diagnosing osteoporosis, it is now clear that BMD alone cannot capture the individual fracture risk. Therefore, several new approaches have been devised to provide a more comprehensive assessment of bone quality. One such approach that has attracted much attention is the trabecular bone score (TBS) [6]. TBS, derived from DXA images, examines the structure of the trabecular microarchitecture and offers indirect information on bone quality. Lower TBS values are associated with a deteriorated microarchitecture and a higher fracture risk, regardless of BMD [6].

Another important advance is high-resolution peripheral quantitative computed tomography (HR-pQCT), which allows the evaluation of bone microarchitecture in three dimensions at peripheral sites, namely, the radius and tibia [7]. HR-pQCT provides a close examination of the trabecular and cortical compartments with parameters such as trabecular number, thickness and separation, and cortical porosity. This imaging modality allows the detection of subtle structural changes that precede measurable reductions in BMD, offering early signs of skeletal fragility. In addition, the use of the so-called finite element analysis (FEA) mathematical model on HR-pQCT scans has improved the ability to estimate bone strength in vivo by simulating mechanical loading conditions.

Magnetic resonance imaging (MRI) techniques [7] are also being investigated for their promise to assess cortical bone quality and water content, essential determinants of the mechanical properties of bone.

Another innovative tool to estimate bone quality is the evaluation of bone material strength index (BMSi) through impact microindentation [8, 9]. This tool directly measures the mechanical properties of cortical bone tissue on the tibial surface and provides information independent of BMD. Lower BMSi values correlate with increased fragility and fracture risk.

Serum and urinary markers of bone turnover, which reflect rates of bone formation and resorption, offer indirect information on skeletal health. An increase in resorption markers, for example, has been linked to an increased risk of fractures even in patients with a relatively normal BMD [10].

Machine learning and artificial intelligence (AI) strategies are also beginning to transform bone fragility testing [11]. By integrating complex images, clinical risk factors, and laboratory data, AI algorithms can develop predictive models of fracture risk that surpass conventional approaches, such as FRAX, an algorithm that can integrate BMD with clinical risk factors, such as age, previous fractures, and family history, to better estimate an individual's fracture risk. FRAX stands for Fracture Risk Assessment Tool and predicts the risk of fracture in a person with osteoporosis over the next 10 years.

These new technologies can offer personalized risk estimation and optimize treatment options.

3 Hormones and Bone

Hormones play a key role in the regulation of bone homeostasis, influencing both resorption and formation. The regulation of bone metabolism, particularly the balance between resorption and formation, is a sophisticated process in which systemic and local factors are closely coordinated and in which hormones are significant modulators. Some of the most important hormones that influence bone are parathyroid hormone (PTH), vitamin D, estrogen, androgen, growth hormone (GH), insulin, and thyroid hormones. All of these regulate particular cellular targets within bone tissue and any alteration in their levels or signaling pathways can compromise skeletal integrity, leading to decreased bone mass, altered microarchitecture, and, ultimately, an increased risk of osteoporosis and fragility fractures [3].Estrogens and androgens play particularly important roles in the acquisition and maintenance of bone mass. Similarly, testosterone promotes bone formation and mineralization. GH and insulin-like growth factor 1 (IGF-1) are also essential during growth and adulthood, as they promote osteoblast differentiation and bone accumulation. Thyroid hormones, particularly triiodothyronine (T3), are central regulators of skeletal development and turnover. They stimulate both bone resorption and formation. PTH and vitamin D also play central roles in calcium-phosphate homeostasis and bone resorption. PTH stimulates bone resorption via osteoclasts to maintain calcium homeostasis, while vitamin D elevates intestinal absorption of calcium as well as controlling osteoblast function. Insulin is an anabolic hormone for bone, enhancing osteoblast activity and collagen synthesis.

In other words, the skeletal system is extremely sensitive to endocrine regulation. Altered hormone levels—due to ageing, chronic diseases, or endocrine disorders—can interfere with the fine balance of remodeling, compromise bone microarchitecture, and increase the risk of osteoporosis and fractures. These hormonal effects must be kept in mind for the prevention and treatment of bone fragility, especially in patients with frequent endocrine diseases, such as diabetes or thyroid diseases.

4 Diabetes and Bone Fragility: Epidemiological Data

Osteoporosis, bone fragility, and increased risk of fractures are now considered common serious complications in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). However, the pathogenetic mechanisms and clinical presentation are significantly different in the two forms of diabetes [3, 5, 12, 13]. In individuals with T1DM, osteoporosis is a long-standing complication. Individuals with T1DM have reduced BMD, a condition mainly due to the onset of the disease early in the years of maximum bone accumulation and lifelong insulin deficiency. Insulin in fact represents a strong anabolic stimulus for bone, and its deficiency results in loss of BMD [3, 5, 12–14]. The meta-analysis by Liu et al. [15] reported that patients with T1DM have significantly more osteoporosis than nondiabetic controls, with an approximately 1.8-fold increased risk. Moreover, the risk of T1DM fractures is significantly higher, with some studies even indicating a relative risk of hip fractures six times higher than in the healthy population [3, 5, 13]. However, in patients with T1DM, the average risk of fractures appears to be increased 3.16-fold, as reported by a recent meta-analysis [16]. This increase in fracture risk appears to be disproportionate to the degree of BMD loss and underlines the contribution of other pathogenetic factors besides insulin deficiency [13, 14].

In contrast, patients with T2DM generally have a normal or even elevated BMD, a situation that has led to their fracture risk being underestimated in the past. Paradoxical as this increase in BMD may be, some population-based research has shown that patients with T2DM acquire a significantly higher risk of fracture, particularly hip and vertebral fractures [17, 18]. Importantly, T2DM is still associated with increased fracture risk after adjustment for BMD and BMI, suggesting that bone quality rather than quantity is predominantly compromised [3, 5, 13]. However, Liu et al. indicated that the prevalence of osteoporosis in groups with T2DM varies strongly with age, gender, and ethnicity and ranges from 7% to over 50% in different subgroups [15]. Hofbauer et al. describe that the pathophysiology of bone fragility in T2DM involves several mechanisms [13].

5 Mechanisms of Bone Fragility in Type 1 and Type 2 Diabetes

In T1DM, bone fragility is mainly due to insulin deficiency, which inhibits bone formation. Insulin is an anabolic hormone and stimulates osteoblast function; insulin deficiency results in defective bone formation and reduced BMD [14]. Furthermore, in T1DM, chronic hyperglycemia increases the deposition of advanced glycation end products (AGEs) in bone collagen, worsening bone quality and making it more fragile [13].

Furthermore, T1DM is also associated with increased oxidative stress and inflammation, which alter bone remodeling by stimulating osteoclast activity and

inhibiting osteoblast function. Together, these factors explain the increased risk of fractures observed in patients with T1DM [13].

In contrast, T2DM is usually characterized by a normal or high BMD, but patients still have an increased risk of fractures. This paradox suggests that the quality, rather than the quantity, of bone is affected in T2DM. Chronic hyperglycemia leads to the formation of AGEs, which accumulate in bone collagen and adversely affect the mechanical properties of bone. Insulin resistance and hyperinsulinemia can also influence the dynamics of bone remodeling, with the possible effect of increasing bone resorption [13].

Furthermore, T2DM is typically accompanied by obesity, which exerts a negative effect on bone quality through inflammatory pathways. Adipose tissue secretes pro-inflammatory cytokines and adipokines that disrupt bone remodeling and lead to impaired bone strength [19].

However, T1DM and T2DM share some mechanisms of bone fragility, including AGE accumulation, oxidative stress and chronic inflammation. All these factors have an impact on bone remodeling and damage bone quality, resulting in an increased risk of fractures [14]. Finally, in both forms of diabetes, microvascular disease may contribute to bone fragility [20], as seen in other diabetic complications [21].

New mechanisms of bone fragility in diabetes have been recently proposed. Among them, it may of interest to discuss the potential role of C-peptide, and Vitamin D.

For a long time, C-peptide, a 31-amino acid peptide released during insulin synthesis, was considered biologically inert. Current research suggests that C-peptide may have an impact on bone [22]. In fact, current findings have identified the link between C-peptide concentration and BMD. In a cross-sectional study of postmenopausal nondiabetic women, decreased serum C-peptide levels were significantly associated with decreased lumbar BMD, suggesting an insulin-independent effect of C-peptide on bone metabolism [23]. This association may imply that C-peptide may directly influence bone-forming cells and play a role in maintaining bone health. The mechanisms by which C-peptide influences bone health may be multiple. In vitro studies have shown that C-peptide is able to stimulate the ERK1/2 signaling pathway in human osteoblast-like cells, resulting in upregulation of type I collagen and regulation of the receptor-activating nuclear factor kappa-B ligand (RANKL) [24]. These actions increase osteoblast activity and possibly inhibit osteoclast-mediated bone resorption, thereby increasing bone formation and reducing bone loss. An association between low C-peptide and history of fractures was also observed in nondiabetic women [25]. In diabetes, particularly in T1DM, C-peptide deficiency is the hallmark. Animal models provided further clarification on the role that C-peptide may have in bone physiology. Diabetic rats receiving C-peptide replacement therapy had improvements in bone microarchitecture parameters, such as thickness and number of trabeculae, compared with controls [26]. These results suggest that C-peptide therapy may reduce diabetes-induced bone loss. The role of C-peptide in T2DM remains elusive, considering that the high incidence of fracture and the high levels of C-peptide usually are detected in patients

with T2DM. However, a "C-peptide-resistance" cannot be excluded. In conclusion, the therapeutic potential for osteoporosis, especially in diabetes, is vast. By increasing osteoblast activity and modulating bone remodeling pathways, C-peptide may represent a new therapeutic option. However, clinical trials need to be conducted to determine the optimal dosage, safety, and efficacy in human subjects.

Vitamin D is another actor in bone fragility in diabetes. Vitamin D is critical for bone metabolism, calcium homeostasis, and skeletal integrity, and its role in both T1DM and T2DM is increasingly evident in the context of fracture risk. Numerous studies have observed that individuals with diabetes have lower serum concentrations of 25-hydroxyvitamin D [25(OH)D], the major circulating metabolite of vitamin D, which may be one of the several factors involved in impaired bone quality and increased fragility for fractures [27, 28].

In T1DM, vitamin D deficiency is of particular concern because of its early onset and association with autoimmune processes [27.28,29]. It has been shown that vitamin D deficiency may precede the development of T1DM and be involved in its etiology by affecting immune function [27–29]. From a bone perspective, vitamin D deficiency in T1DM exacerbates the already high-risk BMD and microarchitectural damage. Reduced vitamin D levels impair intestinal calcium absorption and disrupt the tight regulation of PTH levels, leading to secondary hyperparathyroidism, with increased bone resorption [13]. Similarly, in T2DM, although patients have normal or even elevated BMD, bone quality is typically impaired, such that the risk of fractures is paradoxically high. Hypovitaminosis D in T2DM has also been associated with inadequate glucose control, increased adiposity and inflammation, which exacerbate bone remodeling processes [27, 28]. Vitamin D receptors (VDRs) are present in osteoblasts and osteoclasts, and vitamin D has a direct action in promoting bone formation and regulating bone turnover. In T2DM, vitamin D deficiency can exacerbate bone weakness through altered osteoblast and osteocyte function and mineralization [15, 27, 28].

Several epidemiological reports have found a correlation between vitamin D deficiency and a higher frequency of fractures in diabetic patients. Vitamin D deficiency is significantly associated with an elevated risk of hip and nonvertebral fractures in diabetic patients, after adjustment for BMD [13]. Proposed mechanisms include impaired bone remodeling, increased AGEs, and reduced muscle strength and balance, which also leads to a risk of falls [13, 27, 28]. In addition, vitamin D is likely to be involved in preventing diabetes itself [29, 30] and complications of diabetes that indirectly affect fracture risk. Diabetic retinopathy and neuropathy, for example, increase the risk of falls, while vitamin D supplementation helps to increase muscle function and reduce the risk of falls in the elderly. For diabetic individuals, these preventive effects are particularly beneficial. Therefore, maintaining sufficient vitamin D levels is critical for fracture prevention in T1DM and T2DM. Screening and correction of deficiency is now recommended by guidelines in patients with risk factors such as inadequate sun exposure, obesity, advanced age, or renal failure. Although further randomized controlled trials are needed to determine the optimal dosage and long-term benefits of supplementation in diabetic patients, evidence supports its use in comprehensive bone health programs.

6 Thyroid Diseases and Bone Fragility

Thyroid hormones directly affect skeletal tissue by regulating the rate of bone remodeling [31]. An excess of thyroid hormones, even at the subclinical level, accelerates bone resorption and shortens the remodeling cycle, which can lead to BMD loss and increased fracture risk [31–33]. Indeed, evidence from large prospective cohort studies shows that subclinical hyperthyroidism is associated with increased rates of BMD loss and increased rates of major osteoporotic fractures, particularly in older individuals [31–33]. Conversely, hypothyroidism can also have a negative impact on bone health, but its effect is more insidious, affecting bone development and altering mineralization, especially during critical periods such as growth or post menopause [34].

7 Hypothyroidism and Bone Fragility

Hypothyroidism, both overt and subclinical, is increasingly considered a critical factor in the deterioration of bone health and the onset of osteoporosis, particularly in elderly populations [31, 32, 34]. Epidemiological data have demonstrated a complex interaction between thyroid hormone status and bone BMD and indicated that both deficiency and excess function of thyroid hormones can compromise skeletal integrity. While the link between osteoporosis and hyperthyroidism has long been established, attention has recently turned to the influence of hypothyroidism, particularly subclinical hypothyroidism, on bone metabolism and the likelihood of fracture.

Subclinical hypothyroidism, defined by elevated serum levels of thyroid-stimulating hormone (TSH) with normal levels of free thyroxine (T4), is very common, especially in the elderly and postmenopausal women. The prevalence increases with advancing age and reaches 15% in some populations [34]. The multi-court prospective study of the Thyroid Studies Collaboration analyzed the association between subclinical thyroid dysfunction and changes in BMD in different populations. The study found no statistically significant association between subclinical hypothyroidism and increased bone loss in both sexes [33]. However, the authors pointed out that the clinical significance of subclinical hypothyroidism may vary with age, sex, menopausal status, and fracture risk at baseline.

Nevertheless, other reviews and observational studies show that overt hypothyroidism can also alter bone remodeling processes [3, 12, 31, 32, 34]. The disease is associated with reduced rates of bone resorption and formation, likely resulting in decreased bone turnover. This may impair the adaptive function of the skeleton and make it even more vulnerable to microdamage accumulation and mechanical failure over time [3, 12]. Furthermore, in manifest hypothyroidism, delayed skeletal maturation and mineralization has been observed in young patients, while in the elderly, long-term disease has been found to cause poor bone quality with higher rates of

fractures. In overt hypothyroidism, bone formation markers and resorption markers can decrease by 30–50% compared to normal levels [34]. Population-based research also provides evidence to support the fracture burden of osteoporosis in cases of thyroid dysfunction. In the context of a large-scale population-based epidemiological study in Catalonia, Spain, the incidence of major osteoporotic fractures, particularly hip fractures and vertebral fractures, was found to be significantly elevated in elderly patients who suffered from comorbidities, including with thyroid disease [35]. Although the study did not unambiguously define the effect of hypothyroidism, it lends credibility to the need to consider thyroid function in the overall assessment of fracture risk.

In conclusion, while subclinical hypothyroidism is unlikely to have a significant or uniform impact on BMD or fracture risk at the population level, overt hypothyroidism is likely to have adverse effects on bone health through mechanisms of reduced turnover and impaired bone strength. Further research is needed to clarify the thresholds at which thyroid dysfunction is clinically important for skeletal outcomes and to offer targeted management strategies for osteoporosis prevention in this setting.

8 Hyperthyroidism and Bone Fragility

Both overt hyperthyroidism and subclinical hyperthyroidism are proven risk factors for osteoporosis and fragility fractures. Thyroid hormones are very sensitive to the skeletal system, and supraphysiological levels—due to clinical hyperthyroidism or subclinical TSH suppression—can lead to increased bone turnover, net loss of bone mass, and decreased bone strength [31, 32, 34]. This has significant implications for the epidemiology of fractures, especially in the elderly and postmenopausal women [3, 12, 34].

In symptomatic hyperthyroidism, increased bone turnover causes a reduced remodeling cycle and insufficient time for proper mineralization, which eventually reduces BMD. Excess thyroid hormones accelerate both bone formation and resorption, but bone resorption predominates, leading to a net loss of bone mass and deterioration of skeletal integrity [34]. Histomorphometric studies show that bone turnover markers, such as serum C-terminal telopeptide (CTX) and procollagen type I N propeptide (PINP), can increase by approximately 50–100% in overt hyperthyroidism compared to euthyroid individuals [3]. This excessive remodeling shortens the bone remodeling cycle and results in incomplete mineralization of newly formed bone, contributing to fragility.

Epidemiological data state that in untreated hyperthyroidism, patients have an extremely increased risk of osteoporotic fractures, particularly in the hip and spine [12, 34]. Patients may experience up to 10–20% reduction in BMD at cortical and trabecular sites, depending on the severity and duration of the disease. In addition, the risk of hip fracture in patients with overt hyperthyroidism may be 2–3 times higher than in euthyroid populations [12].

Subclinical hyperthyroidism, defined by suppressed TSH with normal circulating thyroid hormone levels, is less symptomatic but still biologically active. The large-scale prospective cohort analysis conducted by the Thyroid Studies Collaboration showed that subclinical hyperthyroidism is associated with modest bone loss over time, particularly in postmenopausal women and elderly men [33]. Participants with TSH levels below 0.10 mIU/L had the most rapid BMD loss and increased risk of fractures, while those with mildly suppressed TSH (0.10–0.44 mIU/L) had more variable outcomes [33].

The prevalence of subclinical hyperthyroidism in the population is estimated between 0.7% and 2% and increases with age. Its impact on the skeleton, although less pronounced than that of overt hyperthyroidism, is still clinically important. Surís et al. write that population-based fracture registries highlight the contribution of thyroid dysfunction to the incidence of major osteoporotic fractures. Although their study did not differentiate between thyroid subtypes, it justifies the inclusion of thyroid assessment in global fracture risk assessment [35]. The current reviews also emphasize the importance of recognizing subclinical hyperthyroidism as a potentially reversible cause of bone weakness. A longitudinal study shows that people with low but detectable TSH levels may be helped by early treatment and diagnosis, particularly if they have other fracture risk factors [3].

In general, both manifest and subclinical hyperthyroidism are epidemiologically linked to low BMD and fracture risk. While manifest hyperthyroidism is clearly and directly deleterious to bone, subclinical hyperthyroidism—especially when TSH is repeatedly suppressed—is equally worthy of consideration, at least in elderly or postmenopausal patients. Preventive screening and early intervention on thyroid status may be important for preventing osteoporosis and reducing the risk of fractures.

9 Thyroid Hormone Replacement Therapy and Bone Fragility

Thyroid hormone replacement therapy, in most cases with levothyroxine (LT4), is the treatment of choice for hypothyroidism. While appropriate replacement is intended to normalize euthyroidism and prevent the systemic effects of thyroid hormone deficiency, overtreatment can be harmful, especially to the bones. Longitudinal data show that people with low but detectable TSH levels can be helped by early treatment and diagnosis, especially if they have other fracture risk factors [3]. One of the most critical aspects is the risk of occult TSH suppression due to overtreatment with LT4, which can lead to increased bone turnover and ultimately a higher risk of fractures, especially in postmenopausal and elderly women.

Several studies have highlighted the fine line between achieving therapeutic goals and avoiding iatrogenic subclinical hyperthyroidism. The Thyroid Studies Collaboration reported that subclinical hypothyroidism per se is not significantly

associated with increased bone loss, but that overtreatment, resulting in low TSH levels, could actually increase the risk of fractures in the long term [33]. Similarly, Apostu et al. pointed out that suppressive doses of LT4, even in the below-normal range, can be catabolic to bone unless carefully titrated [35]. This impact is particularly relevant in women over 65 years of age, where long-term LT4 therapy with TSH levels below 0.1 mIU/L has been linked to an increased risk of vertebral and hip fractures. The mechanism is thought to be similar to that of subclinical hyperthyroidism, with accelerated bone resorption and impaired microarchitectural integrity. Therefore, it is necessary to advocate the need to pay attention to TSH levels and avoid over-replacement in patients on LT4 therapy, especially those at high baseline risk of osteoporosis [3, 12].

In conclusion, although LT4 therapy is essential in hypothyroid patients, dose individualization and regular TSH monitoring must be performed assiduously to prevent the risk of overtreatment and its negative impact on bone health and fracture risk.

10 Main Mechanisms of Bone Fragility in Thyroid Diseases

Thyroid hormones are key regulators of bone growth, remodeling, and turnover [31, 32]. Both hypothyroidism and hyperthyroidism, overt and subclinical, have been associated with altered bone metabolism and increased risk of osteoporosis and fractures. The mechanisms that determine the impact of these disorders and their treatments on skeletal integrity are complex and reflect direct hormonal effects on bone cells, altered calcium homeostasis, and systemic effects on muscle function and fall risk [3, 31, 32].

Effects of thyroid hormones on bone remodeling Thyroid hormones—triiodothyronine (T3) and thyroxine (T4)—are required for normal skeletal growth and integrity. They act through the nuclear receptors for thyroid hormones (TRα and TRβ) in osteoblasts and osteoclasts [31, 32]. At physiological levels, T3 promotes osteoblastic differentiation and expression of bone matrix proteins. However, in excess, such as in hyperthyroidism or overtreatment with levothyroxine, T3 promotes both bone resorption and formation, but resulting in a net loss of bone due to the shorter lifespan of osteoblasts compared to osteoclasts [3, 35].

Increased bone turnover in hyperthyroidism Hyperthyroidism is characterized by a condition of high bone turnover. Excess thyroid hormone increases the number and activity of osteoclasts through increased expression of RANKL and decreased osteoprotegerin, resulting in increased bone resorption [31, 32]. Although formation is also stimulated, this is not sufficient to reverse the increase in resorption, resulting in a net loss of bone and a reduction in BMD. This leads to thinning of cortical bone and deterioration of microarchitecture, particularly in load-bearing bones [12]. Subclinical hyperthyroidism with low serum TSH and normal T3 and T4 has also

been identified as responsible for bone turnover, particularly in postmenopausal women. The evidence is somewhat sporadic, but in this group, the risk of fracture has been implicated in some studies as a result of prolonged low-grade bone resorption and small loss of BMD over decades [35].

Hypothyroid dysregulation of bone remodeling On the other hand, overt hypothyroidism is characterized by a state of low bone turnover. Decreased thyroid hormone levels suppress osteoblastic and osteoclastic activities, resulting in decreased bone remodeling [3, 12, 31, 32]. While this appears to be a protective mechanism against bone loss, it paradoxically increases skeletal fragility. Reduced remodeling hinders the replacement of microdamaged bone, which leads to reduced bone quality and strength with preserved or even increased BMD [3, 34]. In addition, hypothyroidism delays skeletal maturation, reduces bone mineralization, and affects bone matrix composition due to age or chronic untreated disease in younger adults or those with long-term untreated disease. In older age groups, reduced metabolic activity in bone cells may increase fragility and susceptibility to fractures [12].

Consequences of thyroid hormone replacement therapy Thyroid hormone replacement with levothyroxine (LT4), in particular, is central to the treatment of hypothyroidism, but can induce overt or subclinical hyperthyroidism when used improperly. TSH suppression due to hypertherapy is a known risk factor for increased bone resorption and reduced BMD, particularly in postmenopausal women, who are also susceptible to osteoporosis [33, 34]. The bone depletion effects of LT4 are mediated by the same mechanisms as excess endogenous thyroid hormone: increased osteoclastic activity, reduced efficiency of bone formation, and reduced remodeling cycles. Suppression of TSH within the lower end of the normal range can also have catabolic effects on bone in vulnerable populations. Long-term suppressive therapy, such as that used in thyroid cancer patients, has been shown to significantly reduce BMD and increase the risk of fractures [3].

Calcium and vitamin D homeostasis Thyroid dysfunction also affects calcium and vitamin D metabolism. In hyperthyroidism, bone resorption releases calcium into the bloodstream, which can suppress PTH and reduce active vitamin D levels, with secondary effects on calcium absorption and bone health. Conversely, hypothyroidism can impair calcium absorption and bone mineralization, further compromising skeletal strength [12].

Muscle weakness and risk of falls Muscle weakness and impaired neuromuscular coordination are common in both hyperthyroid and hypothyroid states. These factors contribute to an increased risk of falls and fragility fractures, especially in the elderly. Hyperthyroid patients often have proximal muscle wasting, while hypothyroid subjects may suffer from myopathy and delayed reflexes. These neuromuscular complications increase the burden of fractures in addition to the effects on the bone itself [12].

11 Association Between Diabetes and Thyroid Diseases

The interaction between diabetes mellitus, in particular type 2 diabetes (T2DM), and thyroid abnormalities has attracted considerable interest in recent years due to their high global prevalence, overlapping pathophysiological mechanisms, and bidirectional relationship. Several studies have examined the epidemiological link and the underlying biological mechanisms, demonstrating that T2DM patients had a significantly elevated risk of acquiring thyroid disease and vice versa, reflecting a multifaceted and clinically relevant relationship between the two endocrine conditions.

Epidemiological studies consistently reveal a higher prevalence of thyroid dysfunction in diabetic patients. In a meta-analysis by Rong et al., the risk of T2DM patients developing thyroid dysfunction is 1.38 times higher than in nondiabetic patients [36]. The prevalence of overt and subclinical hypothyroidism was particularly high in type 2 diabetic patients. In fact, in a meta-analysis with 38 studies, the pooled prevalence of thyroid dysfunction was 20.24% [37]. The pooled prevalence of subclinical hypothyroidism, hypothyroidism, subclinical hyperthyroidism, and hyperthyroidism was found to be 11.87%, 7.75%, 2.49%, and 2.51%, respectively [37].

On the other hand, patients with thyroid diseases seem to have an increased risk of developing diabetes. A recent study with 158,674 patients with thyroid disorders and an equal number of matched patients without thyroid disorders showed that after a 10-year follow-up period, the cumulative incidence of T2DM was higher in patients with thyroid disorders than in those without thyroid disorders. The relative risks for T2DM were 1.34 for hypothyroidism and 1.30 for hyperthyroidism [38].

From a pathophysiological perspective, the relationship between thyroid dysfunction and diabetes is multifactorial in nature and involves hormonal and immunological pathways. Insulin resistance, a feature of T2DM, has been found to influence thyroid hormone metabolism and the hypothalamic-pituitary-thyroid axis. It has been observed that hyperinsulinemia stimulates thyroid tissue proliferation, which can lead to thyroid nodularity [39]. In contrast, thyroid hormone is crucial for glucose metabolism and influences insulin release, hepatic gluconeogenesis, and glucose uptake in the periphery. Hyperthyroidism would result in elevated glucose production in the liver and gastrointestinal absorption of glucose that could exacerbate diabetic hyperglycemia. Hypothyroidism, on the other hand, could reduce insulin sensitivity and glucose utilization in peripheral tissues, thus contributing to glycemic failure and metabolic dysregulation [40].

Autoimmunity represents another key factor in the overlap between diabetes and thyroid diseases. Autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, are more frequently seen in patients with T1DM, due to the common genetic susceptibility based on HLA genotypes and immunoregulatory genes. However, the autoimmune context may favor, albeit less frequently, the development of T2DM [41].

Furthermore, subclinical hypothyroidism has been identified as a prevalent condition in diabetic patients and may influence metabolic outcomes even in the absence of overt symptoms. Although it is often considered a benign condition, emerging evidence suggests that subclinical hypothyroidism in T2DM may be associated with worsening lipid profiles, increased insulin resistance, and increased risk of cardiovascular events [39]. The clinical significance of subclinical hypothyroidism in diabetes remains an area of debate, but its high prevalence warrants a cautious and tailored management approach.

In conclusion, the association between diabetes, particularly T2DM, and thyroid dysfunction is strongly supported by epidemiological and clinical research. Both conditions often co-occur and interact mutually influencing each other through multifactorial mechanisms involving hormonal homeostasis, metabolic pathways, and possibly immune mechanisms. The identification and treatment of thyroid abnormalities in diabetic individuals are important to unify treatment and prevent long-term sequelae, including bone damage. Further research needs to be conducted to clarify the complex interrelationship between these two common endocrine diseases and to guide personalized therapeutic strategies.

12 The Dangerous Triangle

Both thyroid disease and diabetes mellitus are recognized risk factors for increased risk of bone fragility and fractures. Each of these endocrine disorders alone can have an independent negative impact on bone metabolism through unique but sometimes concomitant mechanisms, resulting in reduced bone quality, altered microarchitecture, and impaired skeletal strength. Furthermore, diabetes and thyroid disorders can coexist in the same patient, because they both share common pathophysiological pathways, including hormonal imbalance, metabolic dysfunction, and autoimmune processes. When they coexist, they synergistically accelerate skeletal deterioration, contributing significantly to the risk of osteoporosis fractures and causing a significant clinical burden.

When diabetes and thyroid disease coexist, the cumulative impact on the skeleton can be profound. Hyperthyroidism can worsen the bone quality defects already present in diabetic bone disease, while hypothyroidism can further reduce skeletal strength and repair capacity in an already metabolically compromised environment. In addition, both conditions independently increase the risk of falls—through mechanisms such as diabetic neuropathy, visual disturbances, thyroid-induced myopathy, or arrhythmias—thus aggravating the overall risk of fractures. In these patients, traditional BMD measurements may underestimate fracture risk, as BMD does not fully capture bone quality defects or structural deterioration induced by these conditions.

Therefore, the physician must realize that diabetic patients and those with thyroid diseases constitute a group particularly at risk of osteoporotic fractures. Preventive intervention is needed to minimize this combined risk and preserve

skeletal integrity. Screening for thyroid disease in diabetic patients and vice versa is strongly recommended on a routine basis. Routine monitoring of bone health by DEXA or newer methods, such as TBS or HR-pQCT, may perhaps provide a better assessment of bone fragility in this complex population.

Intervention therapy must be chosen appropriately so as not to cause bone damage. Overtreatment of hyperthyroidism into iatrogenic hypothyroidism is possible, which also damages bone quality. Similarly, in hypothyroid patients, overtreatment with levothyroxine to a suppressed TSH level should be avoided so as not to worsen bone loss. In diabetic patients, treatment with glucose-lowering drugs must consider the potential impacts on the skeleton, including not using thiazolidinediones, which increase the risk of fractures, especially in elderly women.

Lifestyle modification is key to reducing the risk of fractures. Encouraging exercise, maintaining adequate levels of calcium and vitamin D, preventing hypoglycemic attacks that can lead to falls, and implementing fall prevention measures at home are all integral components of a fracture prevention program. Smoking cessation, limiting alcohol use, and strict but safe glycemic control also contribute to skeletal protection.

In individuals at very high risk, pharmacological treatment with antiosteoporotic drugs in the form of bisphosphonates, denosumab, or anabolic agents such as teriparatide should be considered. However, renal function, cardiovascular risk, and drug interactions need to be carefully evaluated, particularly in the elderly with multiple comorbidities.

Together, both diabetes and thyroid disease individually cause bone fragility through multifactorial processes and, when present together, synergistically contribute to fractures. Recognition of this synergy is crucial for the early detection of high-risk individuals and the use of targeted preventive interventions. Systematic screening, accurate therapeutic interventions, and general principles of fracture prevention are the basis for reducing skeletal complications and improving long-term outcomes in patients with these interconnected endocrine disorders.

Questions for Self-Assessment

1. *What are the primary physiological roles of thyroid hormones in bone metabolism?*

   (a) Stimulate the production of collagen in the bones
   (b) Regulate bone mineralization and turnover
   (c) Promote osteoclast activation
   (d) Increase calcium absorption in the intestines

   Correct answer: (b) Regulate bone mineralization and turnover

2. *How does diabetes contribute to bone fragility?*

   (a) By increasing osteoblast activity
   (b) Through the accumulation of advanced glycation end-products (AGEs)
   (c) By enhancing bone collagen synthesis
   (d) By reducing calcium excretion through the kidneys

   Correct answer: (b) Through the accumulation of advanced glycation end-products (AGEs)

3. *What role do osteocytes play in bone fragility in the context of diabetes and thyroid dysfunction?*

   (a) They produce new bone tissue to repair fractures.
   (b) They regulate bone resorption and formation by acting as mechanosensors.
   (c) They inhibit the activity of osteoclasts.
   (d) They accelerate the synthesis of bone matrix proteins.

   Correct answer: (b) They regulate bone resorption and formation by acting as mechanosensors.

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Growth Hormone, Insulin-Like Growth Hormone-I Axis, and Bone Fragility

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Abbreviations

aBMD	Areal evaluation of bone mineral density
BMI	Body mass index
BMPs	Bone morphogenetic proteins
BMSi	Bone material strength index
CTX-I	Carboxy-terminal cross-linking telopeptide of type 1 collagen
DXA	Dual-X-ray absorptiometry
ERK	Extracellular signal-regulated kinases
GH	Growth hormone

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GHR	Growth hormone receptor
GHRH	Growth-hormone-releasing hormone
HR-CBCT	High-resolution cone-beam computed tomography
HR-pQCT	High-resolution peripheral quantitative computed tomography
IGF-1	Insulin-like growth factor-I
IRS	Insulin receptor substrate
JAK	JANUS kinase
L-T4	Levothyroxine
OC	Osteocalcin
OPG	Osteoprotegerin
P1NP	Procollagen type 1N-terminal propeptide
PTH	Parathyroid hormone
QoL	Quality-of-Life
RANKL	Receptor activator of nuclear factor kappa-B ligand
rhGH	Recombinant human growth hormone
RUNX	Runt-related transcription factor
STAT	Signal transducer and activator of transcription
T3	Triiodothyronine
vBMD	Volumetric evaluation of bone mineral density
VDBP	Vitamin-D-binding protein
VFs	Vertebral fractures
Wnt	Wingless

Chapter Introduction: What You Will Learn in This Chapter

This chapter explores the critical role of the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis in skeletal development, maintenance, and aging. It provides an in-depth look at the physiological and pathological effects of GH and IGF-1 on bone remodeling, density, and fracture risk throughout life.

The chapter connects with the broader context of endocrine regulation of bone health and aging, complementing other sections of the book that focus on hormonal influences on metabolism and musculoskeletal integrity.

Learning Objectives

By the end of this chapter, readers should be able to:

- Describe the physiological role of GH/IGF-1 in bone development and maintenance.
- Understand the skeletal manifestations of both GH excess and deficiency.
- Recognize diagnostic and therapeutic approaches in bone diseases associated with GH alterations.
- Interpret imaging and biochemical markers of bone health in GHD and acromegaly.

Definitions

- *GH (Growth Hormone)*: A peptide hormone secreted by the pituitary gland, critical for growth and metabolic regulation, particularly in bone tissue.

- *IGF-1 (Insulin-like Growth Factor-1)*: A hormone produced in response to GH, mediating many of its growth-promoting effects, especially in the skeleton.
- *aBMD/vBMD*: Areal and volumetric bone mineral density, used to assess bone strength via DXA or QCT.
- *BTM (Bone Turnover Markers)*: Biochemical indicators of bone formation and resorption.
- *GHD (Growth Hormone Deficiency)*: A condition characterized by insufficient GH production, leading to impaired skeletal health and increased fracture risk.
- *Acromegaly*: A disorder caused by excess GH secretion in adulthood, resulting in bone overgrowth and skeletal deformities.

Key Points

- Vertebral fractures (VFs) are an early phenomenon of impaired bone health in alterations of GH-IGF-1 axis. Dual-energy X-ray absorptiometry (DXA) bone mineral density (BMD) measurements may not reliably predict VF risk.
- Prompt diagnosis of VFs by a morphometric approach is fundamental owing to their clinical impact and predictive role in further clinical fractures.
- Rapid disease control of acromegaly and GH replacement therapy for growth hormone deficiency (GHD) are crucial for the restoration and maintenance of skeletal health.
- Several novel tools assessing bone quality have been proposed for the prediction of fractures to overcome the limitations of conventional areal BMD measurement.
- Replacement of other pituitary deficiencies, especially sex hormones and vitamin D, should be provided for advanced bone outcomes in GHD.
- Special caution is needed for glucocorticoid and levothyroxine replacement to avoid overtreatment.
- During transition period from pediatric to adult care of GHD, GH replacement therapy should be continued to achieve peak bone mass.

1 Introduction

Bone-forming osteoblasts and bone-resorbing osteoclasts dynamically model and remodel bone tissue, adapting it in response to mechanical, hormonal, and metabolic cues [1]. Pituitary hormones are involved in the regulation of bone homeostasis and pituitary disorders due to either hyperfunction or hypofunction of the gland, leading to severe skeletal damage. Parathormone (PTH)/vitamin D axis is responsible for bone mineralization and altered function of the axis leads to an increased risk of fractures. These observations led to recent discovery of a new field of study in bone metabolism, which is now called as “neuroendocrinology of bone” [1].

The anabolic effects of growth hormone (GH) and insulin-like growth factor-I (IGF-I) in bone regulate longitudinal bone growth, skeletal maturation, and acquisition of bone mass during childhood. Late adolescence and early adulthood are key

periods for the achievement of peak bone mass, which is a significant determinant of later risk of osteoporosis. The precise time of the attainment of peak bone mass is not certain, and it is skeletal-site dependent. The increase in gonadal steroid synthesis at the time of puberty is an important hormonal regulator of bone growth [1]. GH/IGF-1 is also crucial for the maintenance of skeletal architecture during adult life by regulating bone remodeling through a complex interaction of endocrine pathways and acting in an autocrine and paracrine way. In addition, emerging evidence suggests that pituitary hormones may bypass traditional pathways and exert remarkable direct effects on the skeleton [1].

2 GH–IGF-I and Bone

GH, also known as somatotropin, is a single-chain polypeptide of 191 amino acids, physiologically synthesized by the anterior pituitary somatotropic cells in a pulsatile manner [2]. Under a negative feedback system, GH synthesis is modulated by two hypothalamic peptides, namely, growth-hormone-releasing hormone (GHRH), and somatostatin [2]. Most of GH molecules circulate in the blood bound to the growth-hormone-binding protein (GHBP), which results from the proteolytic cleavage of the extracellular domain of the GH receptor (GHR), or from mRNA splicing [3]. IGF-I is a protein of 70 amino acids, produced primarily by the liver under the control of GH, but it can also be synthesized in other tissues, in response to GH or other stimuli [1, 2]. The majority of IGF-I in the blood circulates bound to one of six specific binding proteins, namely, insulin-like growth-factor-binding proteins (IGFBPs), principally in a 150-kDa ternary complex [4]. This complex stabilizes IGF-I levels, prolonging its half-life and modulating its availability to target tissues [5]. When GH binds to GHR, dimerization (which indeed may occur even before GH binding [6]) and internalization of the receptor occur, starting the signaling cascade by the activation of the Janus kinase (JAK) 2, signal transducer and activator of transcription (STAT) [7], and extracellular signal-regulated kinases (ERK) 1 and 2 [8–11], which in turn modulate the activity of runt-related transcription factor (RUNX): this is an intracellular protein required for osteoblast cell differentiation [12, 13].

Besides, GH signaling may be modulated by IGF-I receptor (IGF-IR) activation [14, 15]. IGF-IR is a transmembrane glycoprotein tetramer with ligand-activated tyrosine kinase activity. When IGF-I binds to IGF-IR, the receptor dimerizes and undergoes autophosphorylation, leading to the activation of insulin receptor substrate (IRS)-1 and IRS-2 [16], which intercede the effects of IGF-I on osteoblasts [17, 18]. Different hormones and growth factors control IGF-IR expression and affinity, such as platelet-derived growth factor, glucocorticoids, and 1,25-dihydroxyvitamin D [19].

GH and IGF-I play a key role in ensuring the normal course of bone metabolic processes and, consequently, in assuring bone health [19]. GH directly stimulates proliferation and differentiation of cells of the osteoblastic lineage, by enhancing

osteoblastogenesis and opposing adipogenesis, via the downregulation of the expression of fetal antigen-1 (FA1) and the stimulation of the expression of bone morphogenetic proteins (BMPs), as well as wingless (Wnt) signaling pathway [1]. GH also directly stimulates the differentiated function of mature osteoblastic cells, by enhancing the carboxylation of osteocalcin (OC), a marker of osteoblastic function, and the production and accumulation in the bone matrix of osteoprotegerin (OPG), which inhibits osteoclastogenesis and bone resorption, being a decoy receptor for the receptor activator of nuclear factor kappa-B ligand (RANKL) [1].

Systemic IGF-I is essential to maintain cortical bone structure, while skeletal IGF-I is related to the maintenance of trabecular bone [1]. IGF-I enhances osteoblastogenesis by stabilization of β-catenin, which is a signaling molecule of Wnt pathway [1]. However, IGF-I favors the expression of RANKL, leading to a reduction in OPG expression and consequently stimulating osteoclastogenesis. Finally, IGF-I also stimulates the conversion of 25-(OH) hydroxyvitamin D into calcitriol, by promoting the expression and activity of the enzyme 1α-hydroxylase [19].

3 Acromegaly

Acromegaly is a rare endocrine disease usually due to a pituitary adenoma causing overproduction and overexcretion of GH, with consequent increased circulating levels of IGF-I, which is the main mediator of GH effects on peripheral tissues [20].

Chronic exposure to supraphysiological levels of these hormones provokes the emblematic acral overgrowth and coarsening of facial features, together with other musculoskeletal sequelae, such as arthropathy and carpal tunnel syndrome, and an increased risk for impaired quality-of-Life (QoL) affecting endocrine, metabolic, cardiovascular, respiratory, and oncological comorbidities [21, 22].

Recent evidence demonstrated the deleterious effects of excess chronic GH on bone health.

3.1 Bone Turnover and Calcium Metabolism

Markers of bone formation are direct or indirect products of osteoblast activity, their measurement provides an estimation of osteoblast function during different phases of osteoblastic cells development [25]. A valid marker of osteoblast function is represented by the procollagen type 1 N-terminal propeptide (P1NP), which is the precursor of type 1 collagen and, consequently, it is released into serum by osteoblasts during bone formation [26]. Instead, a reliable marker of bone resorption is the carboxy-terminal cross-linking telopeptide of type 1 collagen (CTX-I), which is the degradation product of type 1 collagen and, therefore, it is secreted during bone resorption [26]. Acromegaly leads to elevated bone turnover markers, which in turn reflects the progression of the disease [1, 19]. Bone turnover is uncoupled in favor

of bone resorption, contributing to bone loss occurring in the disease [27]. Disease remission after surgery or control under medical therapy restore normal bone turnover, but could determine low bone turnover if growth hormone deficiency (GHD) develops being relatively frequent complication after surgery, radiotherapy or GHR antagonist therapies (i.e., pegvisomant) [28], further impairing bone health [29].

The clinical consequences of GH and IGF-I overload on calcium and phosphate metabolism are still doubtful; however, patients with active acromegaly often have mild hyperphosphatemia, a tendency to augmented serum calcium levels, and hypercalciuria [30, 31]. The latter is likely due to increased intestinal calcium absorption induced by calcitriol, but also to increased bone turnover due to GH excess; thus, it could be a marker of bone weakness in these patients [30]. Hyperphosphatemia is related to increased intestinal phosphate absorption caused by calcitriol and to the antiphosphaturic effect of IGF-I, whereas a link with the elevated bone turnover occurring in the disease remains unclear [30, 31]. Noteworthily, excessive GH levels might also increase the vitamin-D-binding protein (VDBP) production, lowering the peripheral bioavailability of vitamin D and influencing the response to vitamin D supplementation [32]. Lastly, high levels of GH and IGF-I might impair PTH pulsatility, increasing the pulse half-duration and the pulse mass [33] (Fig. 1).

3.2 Bone Mineral Density

Osteoporosis is a systemic disease of the skeleton characterized by reduced bone mass and bone quality, resulting in decreased bone strength and consequent increased fracture risk [34].

According to World Health Organization (WHO), currently densitometric diagnostic criteria of osteoporosis is based on technical dual-X-ray absorptiometry (DXA) areal evaluation of bone mineral density (aBMD), compared to the average of healthy adults of the same gender (peak bone mass), expressed by standard deviation (SD) from the mean peak bone mass (T-score) [35].

In postmenopausal women and men older than 50 years old, the WHO diagnostic criteria define normal BMD as a T-score > −1.0SD; osteopenia a T-score between −1.0 and −2.5SD; osteoporosis a T-score ≤ −2.5SD, and severe (or established) osteoporosis when there are one or more fragility fractures [35]. In contrast, in females prior to menopause and in males younger than 50, use of Z-score is preferred, comparing with controls of same age and gender. Thus, a Z-score of −2.0SD or lower is defined as below the expected range for age, and a Z-score > −2.0SD is defined within the expected range for age [35].

The first obstacle of the current clinical approach for bone health evaluation in patients with acromegaly is about the applicability of WHO densitometric diagnostic criteria of osteoporosis in these patients, because acromegaly often occurs in men younger than 50 and in premenopausal women [23]. DXA may overestimate

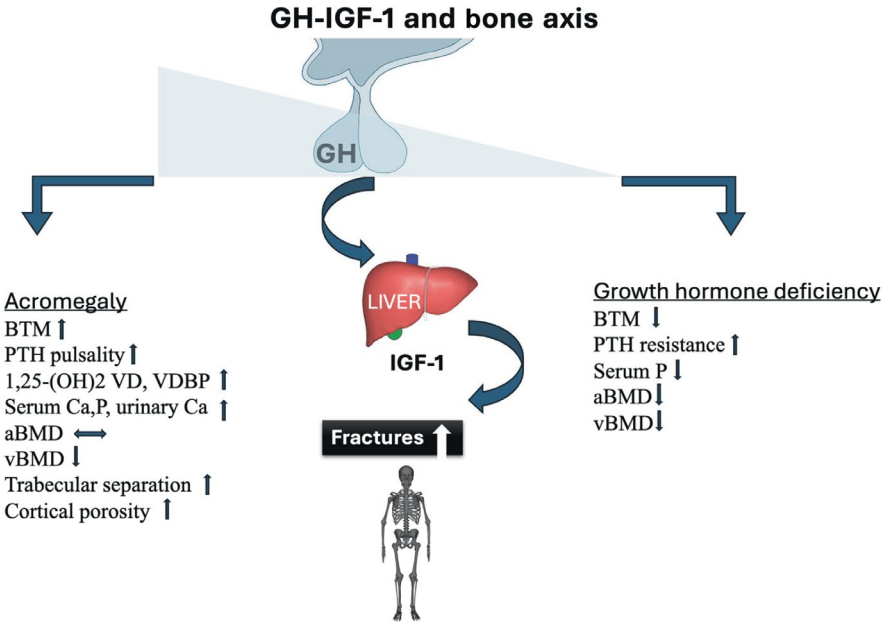

Fig. 1 Effects of alterations in GH and IGF-1 axis on bone health. GH Growth hormone, IGF-1 insulin-like growth factor, BTM bone turnover markers, PTH parathyroid hormone, Ca calcium, P phosphate, VDBP vitamin D-binding protein, 1,25-dihydroxy vitamin D 1,25-(OH)2 VD, aBMD areal bone mineral density, vBMD volumetric bone mineral density

the BMD at the lumbar spine in patients with acromegaly, due to the joint degenerative disorders (exostosis) and the bone enlargement caused by GH excess [36, 37]. The different mechanical demands to skeleton determine the predominance of either trabecular or cortical bone in every skeletal site [38, 39]. Thus, cortical bone is a compact type of bone, mainly found in the shafts of long bones, while the trabecular is a porous foam-like bone, mostly present in the inner part of vertebrae [38, 40, 41]. Excess of both GH and IGF-I typically has opposite effects on bone compartments, damaging trabecular microstructure, while enhancing cortical bone thickness has an effect similar to that of GH on periosteal ossification [19]. Since DXA does not differentiate between cortical and trabecular bone, the measurement of BMD is influenced by the different allocation of bone compartments in the various skeletal sites [42]. As a result, in patients with acromegaly, BMD is typically normal at the lumbar spine and increased at the femoral neck and at the total hip [27] (Fig. 1).

In this specific setting, differently from primary osteoporosis, BMD is not able to predict the risk for fractures, which occur mostly in acromegaly patients with normal or slightly reduced bone mass [27]. Besides, the differences on BMD between the various skeletal sites may be also conditioned by the activity of the disease, due to the opposite impact of pathologically high GH levels on trabecular and cortical bone [36]. During follow-up, patients with controlled disease and concomitant

hypogonadism may experience a reduction in BMD, particularly at the lumbar spine, likely confirming that hypogonadism enhances bone turnover at the trabecular bone [1, 27].

3.3 Vertebral Fractures

Vertebral fractures (VFs) are the most common complication of osteoporosis [43]; however, they frequently occur asymptomatically or without specific symptoms (self-limiting back pain). For this reason, the morphometric approach is mandatory to identify the real prevalence and incidence of these fractures in population studies, as well as in clinical practice [44].

Even though initial studies failed at demonstrating an increased fracture risk in patients with acromegaly [45], likely due to study design biases (using patient-reported questionnaires or inconsistent databases based on radiological medical reports, in which VFs are seldom acknowledged), nowadays, it is well known that VFs are a frequent acromegaly complication, involving about 1 in 3 patients [46], occurring early in the natural history of the disease [47] and being associated with prolonged (>10 years) diagnostic delay [48].

VFs are more frequent in active versus controlled disease, without gender difference, and in hypogonadal versus eugonadal patients [27], occurring more commonly at the thoracic spine, and they are especially anterior wedge fractures [44], likely contributing to the kyphosis of these patients [23] (Fig. 2).

Regarding to incident VFs (i-VFs), over one-third of patients with acromegaly develop them as reported in series with up to 108 months of follow-up [48], in relation to baseline disease status and duration of active disease [44].

Thanks to the medical treatment efficacy, appropriate treatment of acromegaly improves bone health [27], although the risk of VFs may persist high, condition a progression of fractures in some patients with well controlled acromegaly, mostly when pre-existent VFs and hypogonadism are present [49, 50]. In a study evaluating active acromegaly patients despite first generation SRLs undergoing different second-line medical therapies, higher i-VFs were reported in patients with active disease regardless of the therapeutic approach [51]. Nonetheless, a recent report highlighted possible positive effect of pasireotide, a second-line somatostatin multireceptor ligand, independently from disease control, being effective in reducing morphometric VFs also in patients with active disease [52].

Regarding bone-active drugs, including bisphosphonates, denosumab or teriparatide were effective in reducing new VFs incidence in patients with active acromegaly in a retrospective study, their efficacy was not confirmed in those with controlled/cured disease [53]. In this latter condition, hypovitaminosis D could play a major detrimental impact on morphometric vertebral fractures. Since normalization of vitamin D levels (i.e. >30 ng/mL) with cholecalciferol treatment was an independent protective factor, reducing new VFs occurrence [54] (Fig. 2).

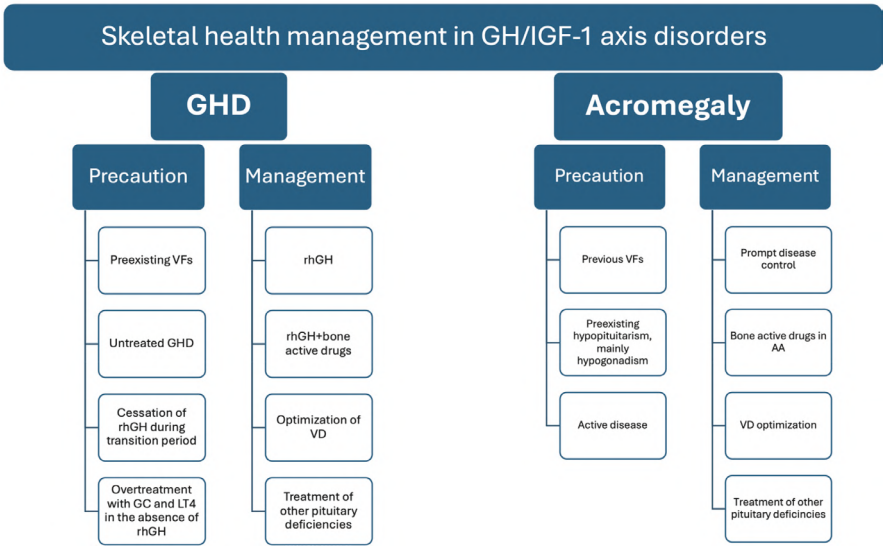

Fig. 2 Skeletal health management in GHD and Acromegaly. VFs vertebral fractures, GHD growth hormone deficiency, rhGH recombinant human growth hormone, AA active acromegaly, VD Vitamin D, GC glucocorticoid, LT4 levothyroxine

3.4 Peripheral Fractures

GH and IGF-I overload is associated with augmented bone mass in skeletal sites with predominant cortical compartment, such as the femoral neck [37, 55–57].

Patients with active acromegaly have a prevalent increase in periosteal bone formation, compared to endocortical bone resorption [41]. This imbalance leads to increased cortical bone thickness of the femoral bone and enlarged bone diameter, as assessed by peripheral quantitative computed tomography (pQTC) [58]. Thus, in a first part of the natural history of acromegaly, patients might have a reduced risk of peripheral fractures [45], due to an augmented bone cortical thickness [58]. Then, the change in biomechanical characteristics of trabecular bone may produce, over time, mechanical stress in the other bone compartments, as in cortical bone of the hip, possibly increasing the risk of fractures in those skeletal sites [41, 59].

Moreover, acromegaly treatments reverse the imbalance of bone metabolism in favor of endocortical bone resorption [41]. Consequently, after starting a GH-lowering therapy, cortical bone thickness tends to reduce, while bone diameter remains enlarged [41]. This potentially results in an impairment of bone geometry of the hip, and then in a reduction of its mechanical strength [41, 60], likely causing the increased risk of hip fractures observed in treated patients with acromegaly [41, 61].

3.5 *Bone Quality Assessment*

The state-of-the-art technique to quantify bone microstructural parameters is high-resolution peripheral quantitative computed tomography (HR-pQCT) at the distal radius and tibia [1, 34]. QCT provides noninvasive 3D measurements of bone geometry, microstructure, and spatial distribution of bone mineral content (BMC), however, with a limited field of view and long scanning time [34, 46]. Even if its role in predicting fractures has been promising, HR-pQCT is substantially used only in research setting, due to high cost, limited availability, and significant ionized radiation exposure [62–64]. A relatively new alternative to HR-pQCT is high-resolution cone-beam computed tomography (HR-CBCT). This scanner has a higher spatial resolution, larger field of view, shorter scanning time, and lower radiation dosage than HR-pQCT [46]; however, the limit of this technique is the reduced image contrast consequent to artifacts [62, 65]. Patients with acromegaly, regardless of VF presence, have lower trabecular bone quantitative parameters, whereas those with VFs have decreased cortical density [60]. Bone microarchitecture impairment is associated with either gonadal status or acromegaly activity, suggesting that a damage of bone microstructure may develop despite of gonadal status [39, 58].

Patients with acromegaly and VFs have lower bone volume to trabecular volume ratio, greater mean trabecular separation and higher cortical porosity than patients without VFs, although without statistically significant differences in mean trabecular thickness and cortical thickness, as assessed by HR-CBCT [66] (Fig. 1). This data have been confirmed also with another non-invasive method, 3D-Shaper, which provides a 3D QCT-like reconstruction of the proximal part of the femur from a standard 2D DXA image, avoids the radiation and the economic costs of a computerized tomography scan [60, 67].

In clinical practice, a simpler and more convenient technique for the assessment of trabecular bone microstructure is the measurement of trabecular bone score (TBS) [1]. TBS is a DXA-derived bone parameter and measures the texture of DXA image at the lumbar spine, as an indirect measure of trabecular bone quality [68]. A high TBS value is suggestive of a healthy trabecular microstructure, whereas a low TBS indicates a damaged trabecular microstructure [34], hence it may predict fragility fractures [46, 69]. TBS values are lower in patients with acromegaly than in control subjects, irrespective of disease activity and gonadal status, and TBS is significantly lower in affected patients with VFs than in those without [70]. Postsurgical remission is associated with higher TBS values, whereas pituitary radiotherapy treatment is associated with lower values [69].

Impact microindentation is a mini-invasive technique, which measures biomechanical properties of cortical bone, by inserting a test probe on the surface of the midtibia [71]. The output of the measurement is called bone material strength index (BMSi). The higher BMSi is, the more resistant cortical bone is to microfracture propagation [71]. BMSi is significantly lower in patients with well-controlled acromegaly, compared to healthy controls [72], indicating that tissue-level properties of

cortical bone remain altered even after remission, probably contributing to the ongoing increased VFs risk [46].

Quantitative ultrasound (QUS) is a low cost and readily available alternative to BMD measurements by DXA. The two main parameters measured by QUS are the speed of sound (SOS) and broadband ultrasound attenuation (BUA). QUS analyses showed that acromegaly leads to a decreased SOS and BUA, which reflect an impaired density, architecture, and elasticity of bones [73].

4 GH Deficiency and Bone Fragility

GHD may cause impaired growth in children and counteract young adults against reaching peak bone mass. The progressive decrease of GH secretion is one of the factors contributing to age-related and postmenopausal bone loss. With the availability of recombinant human GH (rhGH) since 1980s, the treatment was reported to be effective in improving metabolic parameters, BMD, and QoL in GHD [74]. Patients are classified as childhood-onset GHD (CO- GHD) and adult-onset GHD (AO-GHD) [75, 76]. CO-GHD patients suffer from growth impairment and short stature. The most frequent cause of CO-GHD is idiopathic and may not be associated with other pituitary hormone deficiency (PHD). AO-GHD is mainly caused by hypothalamic-pituitary tumors. Importantly, recent emerging number of studies reported nontumoral causes, such as traumatic brain injury, subarachnoid hemorrhage, ischemic stroke, and central nervous system infections [77]. There is no specific biological indicator of GHD in suspected adults as the growth rate of a child. The probability of GHD should be suspected in patients with multiple PHD, since GH secretion is usually the first affected pituitary hormone by pathological causes. We will focus on adult GHD and its detrimental effects on skeletal health.

4.1 Bone Turnover Markers

Patients with GHD have a marked reduction in bone turnover. Histomorphometric analysis of male adult patients with GHD showed decreased osteoid and mineralizing surfaces and decreased bone formation rate [78]. Additionally, decreased serum levels of OC and bone resorption markers confirmed the state of low bone turnover. GHD leads to PTH insensitivity in renal, skeletal, and intestinal cell, causing a mild state of PTH resistance and increased serum PTH levels. Due to the decreased end-organ sensitivity, the calcemic response to PTH is delayed (Fig. 1). Further, abnormalities in the circadian rhythm of PTH related to GHD may alter bone remodeling [1]. GHD is associated with a lower serum phosphate concentration, which is a consequence of a reduced maximal renal tubular reabsorption rate mediated by a lower IGF-I. In addition, abnormalities of renal phosphate handling may affect skeletal health both independently or through its effect on PTH [79].

Increased bone remodeling is observed within a few months of initiation of GH replacement, prior to an increase in bone density is demonstrated. During the first few years of the therapy, both formation and resorption markers increased. Then, bone resorption markers decreased in contrast to bone formation markers [80]. Consistently, the expansion of remodeling space may lead to an initial decrease in BMD during the first year after initiation of GH replacement, with subsequent increase in BMD [81]. Moreover, rhGH causes an increase in serum and urinary calcium after 3–6 months, an effect due to calcium mobilization from the skeleton, an increase in intestinal calcium absorption, and the renal reabsorption of calcium related to increased sensitivity to PTH [1]. In addition, rhGH increases the intestinal absorption of phosphate leading to an increase in serum phosphate levels [79, 82]. During the first months of rhGH replacement therapy, an increase in circulating and cortical bone matrix protein levels of the Wnt signaling antagonist Dickkopf-1 (DKK-1) was reported [83]. Since a positive remodeling balance is achieved at least 12 months after the initiation of GH therapy [84], DKK-1 may contribute to initial increase in bone turnover.

4.2 Bone Mineral Density

Decreased BMD is reported in patients with GHD, either isolated or combined with other pituitary hormone deficiencies [85] (Fig. 1). Patients with GHD exhibit greater losses of cortical than trabecular bone, and this observation is in accordance with the greater effect of systemic IGF-I on cortical than on trabecular bone [86].The degree of bone loss is related to the duration and age of onset of GHD, the severity of the disease, and the age of the patients [1]. Younger patient age and greater severity of GHD also appear to be associated with low BMD in AO-GHD patients. Elderly GHD patients may be less likely to have low BMD z-scores as compared with younger GHD patients. Vertebral BMD is significantly decreased in CO-GHD as compared with AO-GHD [87]. The reason for the different degrees of bone loss may be because CO-GHD occurs before the achievement of peak bone mass, and because the duration of the disease is longer. In CO-GHD, there may be impaired acquisition of bone mass during childhood and adolescence and during the transition period, a period of life occurring between the closure of the epiphyseal plate and the attainment of peak bone mass [1]. A recent retrospective study emphasized that BMD levels were significantly lower in CO-GHD patients compared to AO-GHD patients, besides an overall high frequency of low bone mass in both CO- and AO-GHD patients. CO-GHD, low serum testosterone (T) level, and FT4 were independent risk factors for decreased BMD. The short statue of CO-GHD compared to AO-GHD might contribute to the impaired BMD in the CO-GHD group, since BMD which depends on height and BMD measured by DXA may be underestimated in short of stature patients. The mean BMD and Z-score of CO-GHD patients showed gradual increases through 4 years of follow-up in the same study,

and the rate of change was significantly higher than that of patients with AO-GHD. This may be because the patients with CO-GHD were relatively young, and some patients had not yet reached peak bone value. Therefore, even if rhGH treatment was stopped for various reasons and sex hormone supplementation was continued, BMD continued to increase during follow-up [88]. Also, the presence of additional PHDs, including central hypogonadism, has been shown to be associated with lower BMD among GHD patients [89]. Consistently, an analysis of KIMS database demonstrated that hypogonadal patients were older and had lower IGF-I values and lumbar spine and femoral neck BMD in comparison with sex-steroid-sufficient subjects. In the multivariate analysis, untreated hypogonadism maintained the significant association with BMD at the lumbar spine but not at the femoral neck [90]. A gender-dependent influence of GHD on BMD has been proposed, with affected men having lower BMD than women [91, 92].

4.3 Vertebral Fractures

Several studies reported 2–5-fold increased fracture risk in adults with GHD as compared to control subjects, regardless of the presence of other pituitary hormone deficiencies [93–95]. However, these studies were depended on questionaries or databases that evaluated clinical fractures retrospectively. Morphometric VFs were first evaluated in 2006 in adult patients with GHD showing that VFs were significantly more frequent in this group than control subjects, and VFs were shown to occur in several patients with normal BMD [96] supporting the limited capacity of DXA measurement in prediction of the increased fragility risk in pituitary diseases [1] (Fig. 2). Following morphometric studies supported the increased fracture risk with an up to 50% prevalence of radiological VFs in this clinical setting [89, 97–100]. The occurrence of VFs was dependent on gender, coexistent hypogonadism, and hypoadrenalism advocating that skeletal fragility was sex independent and a general complication of GHD [96]. Interestingly, functional GHD was shown in patients with isolated adrenocorticotropic hormone deficiency, with a complete recovery of GH reserve during glucocorticoid replacement therapy. After describing the transient and reversible GHD in glucocorticoid deprivation, Giustina et al. further demonstrated GH secretion was acutely inhibited by excessive glucocorticoid replacement. This experimental observation provided proof of the biphasic effects of glucocorticoids on GH secretion in humans. Noticeably, GHD per se might predispose patients to glucocorticoid overreplacement as this condition stimulates the activity of 11β-hydroxysteroid dehydrogenase type 1, which increases the exposure of tissues to cortisol [101]. Consistently, in untreated GHD, VFs were more frequent in patients received higher doses than those received lower doses (Fig. 2). In treated GHD patients, however, the prevalence of VFs was not influenced by glucocorticoid treatment doses. The treatment of GHD seems to protect the skeleton from the deleterious effects of glucocorticoid overtreatment in hypopituitary patients [99].

Similarly, a cross-sectional study showed increased prevalence of VFs in patients with central hypothyroidism and coexistent GHD with high replacement doses of levothyroxine (L-T4) treatment. Of note, the association between L-T4 doses and VFs was observed only in patients with treated GHD, whereas when GHD was not treated, the prevalence of vertebral fractures was high regardless of L-T4 doses. It could be hypostasized that GH replacement increases the peripheral activation of T4 to triiodothyronine (T3) potentially resulting in its higher effect at tissue level [98] (Fig. 2). A prospective study showed that more than 40% of patients with untreated GHD developed radiological VFs. The fracture incidence was higher in patients with pre-existing VFs; therefore, screening with spine X-ray in patients is recommended to prevent the clinical progression of osteoporosis [97].

4.4 Bone Quality Assessment

Bone biopsies from male adult patients with GHD reveal decreased osteoid and mineralizing surfaces and decreased bone formation rate. However, a recent study did not find any abnormalities in cortical and trabecular bone microarchitecture and estimated bone strength by HR-pQCT and micro-finite element analysis in adult males with GHD [58]. Indeed, some of these patients had previously received GH replacement 12 months before the study, and this may have counteracted any abnormalities in bone structure and strength at the time of evaluation, consistent with the concept that beneficial effects of replacement therapy may be persistent after rhGH withdrawal [102]. Guidelines drew special considerations pertaining to CO-GHD and the transition to adulthood. Any evaluation of BMD in these patients needs volumetric assessment. Some of these patients may not have reached their true potential maximum bone volume and may continue to increase bone volume with GH therapy. DXA scanning does not directly measure bone volume, although correction formulas can be applied [75]. Consistently, a case–control study, including 20 young male adults with CO-GHD and 30 age- and weight-matched nonathletic healthy men, investigated the bone quality of distal radius and tibia with HR-pQCT. CO-GHD group had significantly decreased total vBMD, cortical vBMD, trabecular vBMD, cortical area, cortical thickness as well as trabecular thickness and trabecular bone volume fraction of both tibia and radius (Fig. 1). Finite element analysis revealed that bone stiffness and failure load of the CO-GHD patients were significantly decreased at both tibia and radius. After adjusting for age, body mass index (BMI) and serum levels of testosterone and f T4, serum IGF-1 level was a positive predictor for total vBMD, cortical vBMD, cortical area, trabecular vBMD, bone stiffness, and failure load of both tibia and distal radius in all subjects. Young adult male patients with CO-GHD who are no longer receiving growth hormone replacement have prominently impaired vBMD and bone microarchitecture and lower estimated bone strength.

4.5 Effect of GH Replacement Therapy on Bone

Many studies have confirmed that rhGH is effective in improving metabolic disorders, low bone mass, and QoL in AO-GHD patient (Fig. 2). Four studies evaluated the long-term effects of rhGH on bone in GHD adults. After an initial decline, all studies reported an increase in both BMD and BMC within the first 5 years of treatment. However, after 5 years, a plateau phase was observed, which lasted for the entire study period [103]. In a prospective study, 15-year GH replacement in AO-GHD induced a sustained increase in total body and lumbar spine BMC and BMD. In femur neck, BMC and BMD peaked at 7 years and then decreased toward baseline values [104]. Another prospective study evaluated the effects of 3-year GH replacement in 45 AO-GHD patients >65 years and in 45 younger control GHD patients. Replacement of GH increased lumbar spine and femur neck BMD and BMC both in younger and elderly GHD patients, supporting the notion that long-term GH replacement is useful also in elderly GHD patients [105].

Several studies showed the favorable effects of rhGH therapy in GHD on fracture risk [1]. A large cohort study assessed the effect of GH treatment on fracture risk in 9641patients with GHD from the international Hypopituitary Control and Complications Study (HypoCCS) surveillance database. The results suggested that GH replacement could protect against fracture in adult patients with GHD but without previously reported osteoporosis [106] and might have shown that BMD could not predict fracture risk in this clinical setting. The effects of GH replacement therapy on fracture risk in different etiologies of GHD were evaluated by the Dutch National Registry of Growth Hormone Treatment in Adults, a nationwide surveillance study. The fracture risk increased in patients previously treated for acromegaly but not in those previously treated for Cushing's disease, compared to severe GHD adult patients using GH replacement therapy due to previous nonfunctioning pituitary adenoma [107]. This could be related to delayed diagnosis of acromegaly, higher radiotherapy rates, and consistent higher PHD rates.

In a prospective study, incidental morphometric VFs occurred more frequently in patients with untreated GHD as compared to treated GHD, advocating the beneficial effects of rhGH on incident VF risk [97]. In another prospective study, BMD scans of lumbar spine were analyzed in a subgroup of patients to obtain TBS. After 2 years of treatment with rhGH, TBS increased of 4% concordantly with positive effect on bone microarchitecture [80]. In a retrospective analysis, GHD subjects with 25 (OH) vitamin D levels below 15 ng/ml had significantly lower IGF-1 levels than those whose 25 (OH) vitamin D was above 15 ng/ml. A prospective study of 57 patients with AO-GHD treated with rhGH for 24 months showed no significant effect of rhGH on TBS in the entire study cohort. However, subjects above 50th percentile of 25 (OH) vitamin D had TBS increase whereas TBS decreased in subjects whose 25 (OH) vitamin D was below the 50th percentile, suggesting sufficient vitamin D levels are necessary for optimal bone outcomes of rhGH [80] (Fig. 2).

After discontinuation of GH therapy that usually occurs at ages 15–17 years old when normal subjects are still increasing bone mass, there is a reduced acquisition

of BMC in early adulthood. An important point is whether therapy should be maintained or reinstituted at least until these subjects reach peak bone mass. All studies except one have demonstrated that continuing/reinstituting GH therapy for periods of up to 2 years in patients who had completed growth resulted in significantly greater BMD than that in patients who had equally severe GHD but received no treatment. Therefore, patients with CO-GHD who have low age-adjusted BMC would benefit from treatment continuation after transition [75]. The possible detrimental effects of stopping GH treatment for more than 18 months during the transition have been highlighted in current guidelines. Thus, if GH treatment is interrupted at this time, retesting and reinstitution of transitional and then adult GH doses should be completed as expeditiously as possible (Fig. 2). DXA measurement of BMD should be evaluated before treatment and at least every 2 years thereafter if it is abnormal [75, 76].

4.6 Effect of Bone Active Drugs in GH Deficiency

Pamidronate attenuated the increase in bone turnover and prevented the decline in BMD that is eventually observed in the first months of GH substitution [82]. A randomized controlled trial compared the effects between rhGH alone and alendronate plus rhGH in GHD adults with osteoporosis. During a 12-month treatment, alendronate induced a significant decrease in serum bone turnover markers. Additionally, lumbar spine BMD increased during rhGH plus alendronate therapy in association with decreased bone turnover markers after 6 and 12 months of follow-up, whereas no changes were observed in patients treated with rhGH alone. There were no changes in femoral neck BMD in either group [108]. Another study observed a plateau in BMD after more than 4 years of GH replacement, and they evaluated the long-term effects of alendronate combination in GHD patients with persistent osteoporosis despite receiving stable rhGH replacement therapy. After 3 years of combined treatment with rhGH plus alendronate, the lumbar spine and femoral neck BMD increased in combination group: this was statistically significant as compared with the patients treated with rhGH alone. Low incidence of VFs was found in the former group [109]. Recently, the advantage of alendronate and GH replacement combination in adult GHD in terms of BMD improvement was proved by the significant increase in BMD and a significant decrease in bone resorption observed in this group compared to GH replacement alone group (Fig. 2). Moreover, attenuation of the rhGH-mediated improvement in renal PTH sensitivity and the increase in renal phosphate reabsorption by alendronate was shown [79].

5 Concluding Remarks and Future Directions

GH and IGF-I axis play a significant role in bone homeostasis and alterations causing either hypersecretion or hyposecretion of these hormones are related to skeletal damage which may lead to impaired QoL and increased mortality. Measurement of BMD is not an useful tool to evaluate skeletal fragility in these clinical conditions. Pre-existing VFs are the most significant predictors of future fractures; therefore, morphometric approach is strongly recommended for bone heath evaluation. Novel bone markers and bone quality assessment have recently gained attention in the clinical management of bone health; however, further studies are needed to establishe their use in routine clinical practice. Prompt disease control of acromegaly and GH replacement therapy in GHD are essential for the restoration and maintenance of skeletal health. Replacement of other pituitary deficiencies, especially sex hormones, should be provided for optimize bone outcomes with special attention to overtreatment of glucocorticoids and L-T4 in patients with GHD. The role of vitamin D for the prevention of VFs in acromegaly and improvement of microarchitecture as combined with rhGH has been proved (Fig. 2). Longitudinal studies are needed in order to understand the effectiveness of bone active drugs for prevention of VFs in both clinical setting.

Questions for Self-Assessment

1. *What is the primary mechanism through which GH influences bone metabolism?*

   (a) Direct stimulation of osteoclast activity
   (b) Indirect effects via IGF-1 on bone formation and remodeling
   (c) Inhibition of calcium absorption
   (d) Suppression of vitamin D synthesis

   Correct answer: (b) Indirect effects via IGF-1 on bone formation and remodeling
2. *Which skeletal feature is most commonly found in adult patients with active acromegaly?*

   (a) Increased trabecular thickness
   (b) Incresed vertebral fracture risk
   (c) Decreased bone mineral density
   (d) Osteonecrosis of the femoral head

   Correct answer: (b) Increased vertebral fracture risk
3. *Which therapy is commonly used to manage skeletal complications in GH deficiency?*
   (a) Bisphosphonates
   (b) Recombinant human growth hormone (rhGH)
   (c) Calcitonin
   (d) Levothyroxine only

   Correct answer: (b) Recombinant human growth hormone (rhGH)

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Bone Fragility in Diabetes: Insights into Mechanisms and Therapeutic Strategies

Malak Faraj and Nicola Napoli

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Chapter Introduction: What You Will Learn in This Chapter
Fragility fractures are a recognized complication of diabetes, increasing patient morbidity and mortality. Patients with type 1 diabetes have reduced bone mineral density, resulting in up to a sixfold increase in fracture risk. Conversely, in type 2 diabetes, fracture risk is increased despite normal or even higher bone mineral density. Thus, additional factors including alterations in bone material properties and bone microarchitecture could have important roles in mediating skeletal fragility in patients with type 2 diabetes. In this chapter, we highlight the latest advances in our understanding of the mechanisms of skeletal fragility in patients with diabetes and discuss potential novel therapeutic approaches that protect bone health in patients with diabetes.

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Learning Objectives
By the end of this chapter, you should be able to:

- Understand the key mechanisms behind bone fragility in diabetes, including molecular and cellular factors.
- Identify how diabetes and its complications, such as microvascular disease and bone marrow adiposity, affect bone structure and function.
- Evaluate the impact of diabetes treatments on bone health, and understand which medications may increase or decrease fracture risk.
- Discuss current treatment strategies for osteoporosis and skeletal fragility in diabetic patients.

Definitions
- Bone Marrow Adiposity (BMAT): The expansion of adipocytes within the bone marrow. Increased BMAT is associated with bone loss and reduced bone strength, particularly in diabetes.
- Advanced Glycation End Products (AGEs): Harmful compounds formed when sugars bind to proteins or fats. In diabetes, AGEs accumulate in the bone matrix, disrupting bone quality and contributing to fragility.
- Microvascular Disease: A complication of diabetes that affects small blood vessels. It can impair blood supply to bones, disrupt bone remodeling, and contribute to increased bone fragility.
- Sclerostin: A protein that inhibits bone formation by blocking the Wnt signaling pathway. Elevated levels of sclerostin are associated with bone loss in diabetes.
- RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand): A cytokine that stimulates osteoclast differentiation and activity, leading to bone resorption. Its production is influenced by inflammation, including that induced by bone marrow adipocytes.

1 Epidemiology of Fracture Risk in Diabetes

The risk of fractures is increased in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) compared with the general population [1, 2]. In a recent meta-analysis, patients with diabetes had a greater risk of total fractures (relative risk [RR] 1.32; 95% CI 1.17–1.48) compared with those without diabetes, and this risk was more pronounced in patients with T1DM (RR 1.51; 95% CI 1.35–1.68) than those with T2DM (RR 1.22; 95% CI 1.13–1.31) [3]. A meta-analysis including around 140,000 subjects with fractures reported that T1DM was associated with a higher risk of total (RR 3.16; 95% CI 1.51–6.63), hip (RR 3.78; 95% CI 2.05–6.98), and spinal fractures (RR 2.88; 95% CI 1.71–4.82) [4].

Among all fracture sites, the risk of hip fractures is particularly increased in patients with T2DM and is further elevated in those with a longer duration of diabetes or those using insulin [5, 6], as well as in those with poor glycemic control [7], which reflects the severity of the disease. Two large meta-analyses, which included

data on more than one million subjects, reported an RR of 1.7 (95% CI 1.3–2.2) [1] and 1.38 (95% CI 1.25–1.53) [8], respectively, for hip fractures in T2DM patients. Moreover, patients with T2DM had an increased risk of nonvertebral fractures (RR 1.19, 95% CI 1.11–1.28) compared to those without diabetes [6]. Other studies focusing on peripheral fractures found an increased risk of foot fractures [9, 10] in patients with T2DM. However, little data is available on vertebral fracture risk in subjects with T2DM. A recent meta-analysis reported a decreased prevalence (odd ratio [OR] 0.84; 95% CI 0.70–0.95) but an increased incidence (OR 1.35; 95% CI 1.27–1.44) of vertebral fractures in patients with T2DM compared with individuals without diabetes [11]. Furthermore, the Iowa Women's Health Study demonstrated an increased risk of vertebral fractures in T2DM women (RR 1.43; 95% CI 1.05–1.97) [12]. However, the Osteoporotic Fractures in Men Study showed that the prevalence and the incidence of vertebral fracture were not higher in men with T2DM than in men without diabetes [13]. These findings suggest that increased vertebral fracture risk might be more frequent in older women with T2DM than in older men with T2DM. Apart from osteoporotic fractures, studies have found that diabetes is associated with an increased risk of atypical femoral fractures [14, 15].

Patients with either T1DM or T2DM, particularly those with diabetes-related complications, display delayed fracture healing and more postsurgical complications, such as wound infections or cardiovascular events, compared to patients without diabetes [16–18]. Importantly, mortality following hip fracture was 28% and 57% higher in men and women with T2DM, respectively, compared with those without diabetes [19]. Moreover, patients with both T2DM and vertebral fractures have been reported to have increased mortality compared with individuals without T2DM or vertebral fractures (HR 2.11; 95% CI 1.72–2.59) or with vertebral fractures alone (HR 1.84; 95% CI 1.49–2.28) [11].

2 Bone Microarchitecture and Strength in Diabetes

Areal bone mineral density (aBMD) measured by dual-energy X-ray absorptiometry (DXA) is currently the gold standard for predicting fracture risk in clinical practice [20]. While this measure is useful for T1DM patients who have decreased BMD, it is challenging for T2DM patients who typically have normal or elevated BMD despite a higher fracture risk [21]. A likely explanation for this paradox is that bone fragility and fracture risk are critically influenced by the cortical and trabecular bone microarchitecture, which may be altered differently in T1DM and T2DM.

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a three-dimensional imaging technique used to assess the bone microarchitecture of the cortical and trabecular compartments in the distal tibia and radius. Results from previous studies have not been consistent, with some [22, 23] but not all [24] reporting increased cortical porosity in T2DM, while trabecular indices were generally preserved or improved. Recently, in the MroS study [25], we found that T2DM men had a smaller total cross-sectional area and cortical area at the tibia, but not the

radius, resulting in decreased estimated bone strength. Overall, cortical porosity was not statistically different between the groups, but we found that patients with a diabetes duration ≥10 years had increased cortical porosity at the radius compared to men with a diabetes duration <10 years, implying that increased cortical porosity may not be characteristic of all T2DM patients, but rather of a subgroup characterized by longstanding diabetes (≥10 years). Notably, cortical thickness is reduced in both T1DM [26] and T2DM [27]. Unlike, in T2DM, a recent meta-analysis identified a decreased trabecular number and increased inhomogeneity of trabecular network in T1DM patients [28]. Moreover, studies have found a smaller cross-sectional area at the tibia or radius in patients with T1DM compared to controls [29, 30].

Another aspect of bone quality that might be compromised in diabetes is the material properties of bone. Using microindentation of cortical bone, a few studies have found a reduced bone material strength index (BMSi) in patients with T2DM compared to controls [24, 31, 32], which could reflect alterations in collagen crosslinks by advanced glycation end products (AGEs) and changes in mineralization [33].

Although patients with diabetes might have alterations in bone quality, heterogeneity could exist within these patients. This heterogeneity could be related to the underlying diabetic complications, which might vary from one cohort to another.

3 Mechanisms of Skeletal Fragility in Diabetes

The pathophysiological mechanisms underlying bone fragility in diabetes are complex and not fully understood. These mechanisms include, but are not limited to, low bone turnover, accumulation of AGEs that alter collagen properties, osteocyte dysfunction and senescence, increased SOST production, inhibition of Wnt signaling, increased bone marrow adiposity, inflammation, the presence of diabetic complications such as microvascular disease, and potential side effects of diabetes medications [34].

3.1 Low Bone Turnover

Bone remodeling, which involves the coordinated actions of bone-resorbing osteoclasts and bone-forming osteoblasts, is essential for continuous bone turnover [35]. Low bone turnover has been established as a typical aspect of diabetes, as indicated by biochemical markers or histomorphometry findings. Similar to T1DM, most studies have reported reductions in serum levels of the bone resorption marker C-terminal telopeptide of type I collagen (CTX-1), as well as in the bone formation markers procollagen type 1 amino-terminal propeptide (P1NP) and osteocalcin, in patients with T2DM than nondiabetes subjects [36–39]. Although bone histomorphometry is the gold standard approach to assess bone remodeling, bone biopsy studies in patients with diabetes are sparse and have included relatively small numbers of patients. Reduced histomorphometric indices of bone formation, including mineralization surface, mineral apposition rate, bone formation rate, and adjusted

apposition rate, were observed in patients with diabetes (six with T2DM and two with T1DM) compared to controls [40]. In another study, reduced mineralizing surfaces, bone formation rate, and osteoblast surface were found in patients with T2DM compared to those without diabetes [41]. In contrast, no differences were observed in bone histomorphometric indices in T1DM patients compared to controls; however, patients in this study had well-controlled HbA1c levels (<7%) [42].

3.2 Accumulation of Advanced Glycation End Products

Alterations in bone quality in both T1DM and T2DM might be due to AGEs accumulation. Levels of AGEs are increased in patients with diabetes as a result of hyperglycemia [43]. Accumulation of AGEs creates nonenzymatic cross-links with type 1 collagen (the main protein in bone), which reduces the material properties of bone by stiffening the bone collagen and reducing bone strength [44, 45]. In addition to their effects on bone material properties, AGEs also bind to their receptor (RAGE), resulting in changes in the function of bone cells. In vitro studies have shown that AGEs reduce osteoclast differentiation and activity [46] and suppress osteoblast function as well [47], indicating that they might contribute to the low bone turnover condition in diabetes. Due to the invasive nature of bone biopsies required for the direct measurement of bone AGEs, alternative methods were developed to assess AGEs in serum, urine, and skin. Importantly, in a clinical study, our group reported that AGEs deposition on human femoral heads was almost doubled in patients with T2DM compared to those without diabetes and was associated with impaired bone microarchitecture [48]. Moreover, a recent study that characterized femoral cortical bone in patients with T2DM reported that higher levels of N-carboxymethyl-lysine (a well-characterized AGE) detected in these patients were associated with increased cortical porosity [49]. Interestingly, negative correlations between pentosidine, a well-characterized AGE, and trabecular bone score (TBS) were observed in patients with T2DM [50]. Similarly, skin AGEs were negatively associated with BMSi in patients with T2DM ($r = -0.30$, $P < 0.001$) [51]. Thus, higher amounts of AGEs in diabetes might result in an increased fracture risk. In a study of older men and women with and without diabetes (Health ABC study), higher urinary pentosidine levels were associated with a higher vertebral fractures risk in patients with T2DM than those without T2DM [52]. Moreover, in a cross-sectional study, serum levels of pentosidine were associated with prevalent fractures in T1DM independently of BMD [53].

3.3 Osteocytes Dysfunction and Senescence

The low bone formation rate observed in diabetes suggests that, in addition to its direct negative effect on osteoblasts, diabetes may also affect the function of osteocytes. Osteocytes are cells that sense mechanical loading and structural microdamage within the bone matrix with their canalicular network and

orchestrate bone remodeling by regulating both osteoblast and osteoclast function [54]. A recent study linked microdamage accumulation due to impaired bone remodeling to more severe disruption of osteocyte canaliculi around microcracks and a higher osteocytes apoptosis rate in streptozotocin-induced T1DM rats, leading to reduced bone strength [55]. Recently, several studies have shown that diabetes affects osteocyte communication by reducing RANKL secretion, which suppresses osteoclast recruitment and bone resorption, while simultaneously increasing sclerostin production, thereby inhibiting bone formation [55, 56]. Interestingly, Shao et al. revealed that pulsed electromagnetic field exposure suppressed the detrimental consequences of diabetes on osteocyte apoptosis and sclerostin expression in a T2DM mouse model, consequently improved bone quality, suggesting that stimulating osteocytes may mitigate bone fragility [57]. In addition, a recent study in an inducible obese mouse model of T2DM found increased accumulation of senescent osteocytes in bone with a unique proinflammatory profile, reflecting accelerated cellular aging [58]. Regarding their skeletal phenotype, these mice displayed several alterations in bone quality that closely mirror those observed in patients with T2DM, including compromised cortical bone microarchitecture, reduced biomechanical strength, and impaired bone material properties. These findings provide a novel mechanism for targeted therapy.

3.4 Increased Sclerostin Production

Sclerostin, a glycoprotein encoded by SOST, is secreted by osteocytes and inhibits osteoblast activity by suppressing the canonical Wnt/β-catenin signaling pathway [59]. It also promotes osteoclast activity by stimulating the release of receptor activator of nuclear factor-kB ligand (RANKL) from osteocytes [60]. In vitro studies have shown increased sclerostin expression in osteocytes after incubation with high glucose concentration [61–63]. Studies in rodents [64, 65] and humans [36, 66–68] have found that sclerostin levels were increased in T1DM and T2DM compared to controls. Similarly, in a clinical study, our group showed increased SOST gene expression in bone tissue of T2DM patients compared to patients without diabetes [48]. Interestingly, sclerostin was positively correlated with glycated hemoglobin (HbA1c) and duration of T2DM [69, 70], and inversely associated with bone formation markers and bone turnover [67, 71]. In terms of fracture risk, higher levels of sclerostin were associated with an increased risk of fragility fractures in patients with T2DM [72–74]. Conversely, sclerostin levels were inversely associated with fracture risk in patients with T1DM [75]. Importantly, the determinantal effects of T1DM and T2DM on the skeleton were reversed with sclerostin blockade [76, 77]. Taken together, it appears that changes in sclerostin levels in diabetes may result from osteocyte dysfunction due to hyperglycemia, reduced mechanical loading, and other potential factors.

3.5 Inhibition of Wnt Signaling

Wnt signaling pathway plays an important role in bone homeostasis. Wnt signaling promotes mesenchymal stem cell (MSC) differentiation into osteoblasts by inducing the expression of osteogenic transcription factors Runx2 and osterix [78, 79], while it prevents adipocyte differentiation by inhibiting the expression of the adipogenic factors CCAAT/ enhancer-binding protein α (C/EBP α) and peroxisome proliferator-activated receptor γ (PPAR-γ) [80]. Canonical Wnt signaling is also important for regulating osteoclastogenesis. Activation of Wnt signaling suppresses osteoclast differentiation by inducing Osteoprotegerin (OPG) expression. OPG is secreted by osteoblasts and osteocytes and inhibits osteoclastogenesis by preventing the interaction of RANKL with RANK to suppress bone resorption [81].

While glucose is a crucial energy source for osteoblasts [82], hyperglycemia impairs osteogenesis [83, 84] by enhancing the production of Wnt signaling inhibitors, mainly sclerostin and Dickkopf-1 (DKK-1) [85]. Recently, we showed that the gene expression of Wnt antagonists SOST and glycogen synthase kinase-3 β (GSK3B) was higher, while the gene expression of Wnt agonists lymphoid-enhancer-binding factor 1 (LEF-1) and WNT10B was lower in bone tissue of T2DM patients compared to those without diabetes [70]. Besides elevated sclerostin, DKK-1 is also increased in patients with T1DM and T2DM [86, 87]. Accordingly, targeting the Wnt/β-catenin signaling pathway could be an ideal treatment strategy for diabetes-associated bone loss. Unlike sclerostin [88], Hildebrandt et al. reported that the deletion of osteogenic Dickkopf-1 in mice partially prevented T1DM-induced bone loss by regulating the number of osteoclasts due to a compensatory increase in sclerostin [89]. Therefore, antibodies targeting both DKK-1 and sclerostin simultaneously might be a more effective strategy to counteract bone loss in diabetes. Moreover, several previous studies have reported that direct activation of Wnt signaling through constitutive activation of β-catenin in osteoblasts ameliorated diabetic bone disease in mice with T1DM [90–92].

3.6 Bone Marrow Adiposity and Adipose Tissue Inflammation

Expansion of bone marrow adipose tissue (BMAT) could be one of the key pathogenic mechanisms underlying diabetic bone fragility. Previous studies have reported increased BMAT in both T1DM and T2DM [93–95]. BMAT originates from bone marrow mesenchymal stem cells (BM-MSC), which give rise to adipocytes or osteoblasts [96]. This process is tightly regulated by various factors present in the bone marrow microenvironment, including secreted proteins and transcription factors (e.g., PPARγ, sFRP1, Runx2, Wnt, adiponectin) that determine the commitment of BM-MSCs to the adipocyte or osteoblast lineage depending on the physiological needs of the organism. However, increased levels of oxidative stress and senescence within the bone environment in diabetes disrupt the balance between

BM-MSCs and their commitment, favoring adipogenesis over osteogenesis [97]. Animal studies have shown that increased BMAT in mice with induced diabetes is associated with bone loss [94, 98]. Furthermore, a positive correlation between sclerostin and BMAT accumulation was observed in patients with T2DM, suggesting that osteocyte activity may influence bone marrow fat [99].

Increasing evidence suggests that bone marrow adipocytes play a critical role in altering the bone microenvironment in diabetes. Bone marrow adipocytes secrete various pro-inflammatory cytokines and adipokines [100, 101] that enhance osteoclast activity and promote bone resorption by stimulating the production of the osteoclastogenic cytokine RANKL [102]. Wang et al. reported that IL-6 KO mice were protected against HFD-induced trabecular bone loss and the associated BMAT expansion [103]. Similarly, Zhang et al. reported that exosomes from adipose-derived mesenchymal stem cells inhibited the secretion of IL-1β and IL-18 by suppressing the NLRP3 inflammasome in high-glucose-treated osteoclasts and restored bone loss in streptozotocin-induced diabetic osteoporotic rats [104]. In addition, the deletion of adipsin, a dominant adipokine during BMAT expansion in both mice and humans, inhibited BMAT expansion and improved bone mass in mouse models of caloric restriction and thiazolidinedione-treatment-induced bone loss by activating Wnt signaling [105].

3.7 Microvascular Disease

Microvascular disease, a common complication of diabetes caused by hyperglycemia, contributes to skeletal fragility in diabetes [106, 107]. Histological analysis of bone remodeling units has identified the presence of a capillary system that supplies these units with blood, nutrients, growth factors, and other cells needed for bone growth and remodeling [108]. Disruptions in the interaction between the vasculature and bone remodeling compartments can lead to impaired bone homeostasis, as seen in diabetes [109].

Clinical studies using HR-pQCT imaging have found increased cortical porosity in patients with T2DM [28], which appears to be most pronounced in those with prevalent microvascular disease. A study by Shanbhogue et al. [110] found that T2DM patients with retinopathy, nephropathy, or neuropathy had higher cortical porosity at the radius, with a trend toward higher cortical porosity at the tibia compared to patients without microvascular complications, suggesting that microvascular disease may impact bone microarchitecture. Along with this finding, a cross-sectional study using HR-pQCT has demonstrated that reduced microvascular blood flow due to peripheral vascular disease is associated with increased cortical porosity at the distal tibia in patients with T2DM [51]. Similarly, high-resolution imaging studies showed increased cortical porosity in T1DM patients with neuropathy compared to controls [111]. The precise cellular mechanism connecting microvascular disease and increased cortical porosity remains to be defined, but impaired crosstalk between the bone vasculature, such as vascular endothelial cells and

osteogenic precursor cells, could be a potential mechanism [112]. Decreased vascularization due to microvascular disease would impair the recruitment of osteogenic precursor cells from blood vessels [113]. By impairing cell recruitment, microvascular disease would hinder bone formation at sites of intracortical remodeling, resulting in the formation of cortical pores. However, further studies are needed to understand how microvascular disease contributes to bone fragility in diabetes.

4 Impact of Diabetes Mellitus Medications on Fracture Risk

Evidence from epidemiological studies and clinical trials in diabetes has provided important insights into the possible beneficial or adverse effects of antidiabetic medications on fracture risk. Metformin, the first-line treatment for T2DM, has been reported in several clinical studies to have either a positive [114, 115] or neutral [116–119] effect on BMD and fracture risk among patients with T2DM. Similarly, incretin-based drugs, including dipeptidyl peptidase inhibitors (DPP-4) and GLP-1 receptor agonists [120–123], have a neutral effect on bone without increasing fracture risk. Interestingly, a meta-analysis of 38 randomized clinical trials involving 39,795 patients with T2DM reported that both liraglutide and lixisenatide were associated with a significant reduction in fracture risk compared to placebo and other antidiabetic drugs [124]. By contrast, sodium/glucose cotransporter 2 (SGLT2) inhibitors, specifically canagliflozin, should be cautiously prescribed in patients with T2DM, as this drug has been associated with an increased fracture risk [125]. However, a recent meta-analysis, which included 27 randomized controlled trials with a total of 20,895 T2DM participants and an average study duration of 64, 22 weeks, did not find an increased fracture risk in patients treated with SGLT2 inhibitors [126]. More long-term follow-up data are required to clarify the impact of SGLT2 inhibitors on fracture risk. Although sulfonylureas are widely used as a second-line treatment, they should be avoided in patients with T2DM at increased fracture risk [127, 128]. In the MrOS study, Napoli et al. found a 66% higher nonvertebral fracture risk in men with diabetes using sulfonylureas compared to normoglycemic men [119]. Despite the beneficial effect of thiazolidinediones on insulin resistance, their use should also be avoided, as these drugs are associated with an increased fracture risk among patients with T2DM [129].

Insulin remains the only treatment option for T1DM and often becomes necessary over time in T2DM as the disease progresses. Recently, we showed that men with T2DM who are using insulin had lower bone strength and impaired cortical bone microarchitecture compared to noninsulin users [25]. Moreover, several studies have reported an increased fracture risk in diabetic insulin users compared to noninsulin users [119, 130]. However, the increased fracture risk among insulin users is more likely due to diabetic chronic complications, which may trigger a more aggressive therapeutic approach in elderly individuals, resulting in a greater rate of hypoglycemic events and, in turn, an increased risk of falls and fractures [131].

5 Treatment of Skeletal Fragility in Diabetes

Lifestyle interventions are the cornerstone of T2DM management [132]. Dietary interventions that improve glucose metabolism might concurrently improve bone health in diabetes [133, 134]. However, weight loss alone and reduced skeletal load impair bone health and increase the risk of fragility fractures [135–137]; therefore, it must be combined with exercise training [138, 139]. Indeed, previous findings have shown that exercise training prevented the weight-loss-induced increase in sclerostin, consequently attenuating bone loss and preserving bone geometry in elderly obese individuals [135].

Studies evaluating the effect of antiosteoporotic medications in patients with T1DM and T2DM are sparse, and so far, current evidence is based solely on post hoc analyses of randomized trials. In the Fracture Intervention Trial (FIT), 3 years of alendronate treatment (a potent antiresorptive drug) yielded a similar BMD gain and safety/tolerability profile in women with T2DM compared to those without diabetes [140]. Additionally, a meta-analysis evaluating osteoporosis drugs, including bisphosphonates, reported that the effect of alendronate on BMD gain and vertebral fracture risk reduction was not affected by diabetes status [141]. For denosumab, post hoc analysis from the FREEDOM trial showed that in women with postmenopausal osteoporosis and diabetes, denosumab treatment reduced vertebral fracture risk by 80% compared to placebo [142]. However, it increased the risk of nonvertebral fractures by 90%. Notably, this effect was observed only in the first 3 years of the study and not during the 10-year extension; thus, the impact of denosumab on nonvertebral fracture risk in diabetes remains unclear.

Given the low bone turnover in patients with diabetes, anabolic therapy could be a promising alternative to antiresorptive drugs. Supporting this, an analysis of four prospective observational studies, including 8828 patients with osteoporosis, found that the effects of teriparatide on fracture risk are similar in patients with and without diabetes after 6 months of treatment [143]. Post hoc analysis of the ACTIVE trial involving 198 postmenopausal women with T2DM showed that abaloparatide significantly improved BMD and trabecular bone score compared with placebo [144]. Romosozumab, a new potential anabolic therapy that targets sclerostin, has been shown to increase BMD at the lumbar spine, total hip, and femoral neck, and reduce the risk of vertebral, nonvertebral, and hip fractures compared to placebo [145]. As increased sclerostin levels in diabetes may contribute to bone disease, it will be interesting to investigate the effect of romosozumab in patients with diabetes.

Finally, ensuring adequate intake of calcium and vitamin D is essential for the prevention and treatment of osteoporosis in patients with diabetes [146]. In the absence of further evidence, antiresorptive treatment with either bisphosphonates or denosumab remains the first choice for osteoporosis treatment in patients with T2DM, considering comorbidities, renal function, and patient preference [147].

6 Conclusions

Patients with diabetes are at an increased risk of fragility fractures. In Type 2 diabetes, BMD is increased, but in both type 1 diabetes and type 2 diabetes, bone quality is impaired. Although type 1 diabetes and type 2 diabetes have different pathogenetic patterns, long-term disease is associated with low bone turnover, accumulation of AGEs in the bone matrix, impaired Wnt signaling, bone marrow adiposity, a proinflammatory state, and microvascular impairment, all of which impair bone cell activity and bone repair. The clinical evidence regarding the efficacy and safety of antiosteoporosis treatments in diabetic patients is based on post hoc subgroup analyses of randomized clinical trials that primarily enrolled osteoporosis patients. Prospective randomized controlled trials are needed to assess the efficacy of osteoporotic treatments in improving microstructure and fracture risk in patients with diabetes and fragility fractures.

Questions for Self-Assessment

1. *What is the primary pathogenic mechanism underlying diabetic bone fragility?*

   (a) Excessive bone formation
   (b) Bone marrow adiposity and inflammation
   (c) Increased bone mineral density (BMD)
   (d) Elevated calcium absorption

   Correct answer: (b) Bone marrow adiposity and inflammation
2. *Which diabetes medication has been associated with an increased risk of fractures?*

   (a) Metformin
   (b) SGLT2 inhibitors (e.g., canagliflozin)
   (c) GLP-1 receptor agonists
   (d) Dipeptidyl peptidase inhibitors (DPP-4 inhibitors)

   Correct answer: (b) SGLT2 inhibitors (e.g., canagliflozin)
3. *What role does sclerostin play in diabetic bone disease?*

   (a) Promotes bone formation
   (b) Inhibits bone formation
   (c) Stimulates osteoclast differentiation
   (d) Increases bone marrow adiposity

   Correct answer: (b) Inhibits bone formation

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Study of the Basal Metabolic Rate in Thyroid Dysfunctions and Diabetes

Laura Vitale, Stefano Massarini, and Anna Ferrulli

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Chapter Introduction: What You Will Learn in This Chapter
In this chapter, we delve into the relationship between thyroid dysfunction and metabolism, specifically focusing on energy expenditure and its connections with conditions such as diabetes. You will learn how thyroid hormones influence metabolic processes, how hypothyroidism and hyperthyroidism impact energy balance, and the implications for patients with diabetes and obesity. Key topics include the role of thyroid hormones in energy expenditure, the effect of thyroid dysfunction on weight management, and the potential metabolic alterations in hypothyroid patients despite standard treatment. By the end of this chapter, you will have a better understanding of the thyroid axis's role in regulating metabolism and energy expenditure and its implications for managing metabolic disorders.

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Key Points
- The relationship between thyroid hormones and energy expenditure
- The effect of hypothyroidism and hyperthyroidism on metabolism
- The impact of thyroid disorders on diabetes and obesity
- Metabolic consequences of levothyroxine replacement therapy
- The syndrome of resistance to thyroid hormone and its effect on metabolism

Learning Objectives
By the end of this chapter, you will be able to:

- Understand the role of thyroid hormones in regulating energy expenditure and metabolism.
- Identify how thyroid dysfunction, including hypothyroidism and hyperthyroidism, impacts metabolic rates and body weight.
- Discuss the implications of thyroid disorders in patients with diabetes and obesity.
- Evaluate the effectiveness of levothyroxine therapy and its limitations in correcting metabolic alterations in hypothyroid patients.
- Recognize the syndrome of resistance to thyroid hormone and its effects on energy expenditure.

Definitions
- Thyroid Hormones (THs): Hormones produced by the thyroid gland (primarily T3 and T4) that regulate various bodily functions, including metabolism, energy production, and growth.
- Resting Energy Expenditure (REE): The amount of energy expended by the body at rest, crucial for maintaining basic physiological functions like breathing, circulation, and cellular activity.
- Hypothyroidism: A condition in which the thyroid gland does not produce enough thyroid hormone, leading to a slowed metabolism, weight gain, and other symptoms.
- Hyperthyroidism: A condition in which the thyroid gland overproduces thyroid hormones, leading to a sped-up metabolism, weight loss, and other symptoms.
- Levothyroxine: A synthetic form of the thyroid hormone T4 used to treat hypothyroidism.
- Syndrome of Resistance to Thyroid Hormone (RTH): A genetic condition caused by mutations in the thyroid hormone receptor, leading to reduced sensitivity to thyroid hormones and altered metabolism.

1 Effects of Thyroid Hormones on Glucose Metabolism

Thyroid disorders are more prevalent in patients with both type 1 and type 2 diabetes [1] compared to the general population, and conversely, a higher prevalence of diabetes is detectable in individuals with thyroid disorders (both hypothyroidism and hyperthyroidism) [2, 3].

Autoimmunity is key to understanding the link between type 1 diabetes and autoimmune thyroid diseases, with this combination recognized as autoimmune polyglandular syndrome type 3 (APS-3) variant. On the other hand, the relationship between thyroid disorders and type 2 diabetes is more complex, as both hyperthyroidism and hypothyroidism can be risk factors for hyperinsulinemia and glucose intolerance. A deficiency in thyroid hormones is also a risk factor for obesity, dyslipidemia, and metabolic syndrome, in addition to type 2 diabetes, whereas thyroid hormone supplementation has been reported to improve insulin sensitivity [4, 5].

Although insulin and glucagon are the main regulators of glucose metabolism, thyroid hormone (TH) has long been known to influence glucose homeostasis by acting on multiple organs, including the liver, gastrointestinal tract, pancreas, adipose tissue, skeletal muscles, and central nervous system [6].

Several studies have shown that thyroid hormone affects pancreatic β-cell development. Specifically, triiodothyronine promotes the differentiation of pancreatic ductal cell lines into a β-cell phenotype. MAFA, one of the essential transcription factors for β-cell maturation, was shown in a 2013 in vivo trial to have a functional receptor-ligand interaction with TH at the MAFA promoter, leading to enhanced expression and improved glucose responsiveness in neonatal β-cells [7]. Using pancreatic islets isolated from postnatal rats, researchers demonstrated that expression of thyroid hormone receptors develops in parallel with age and glucose responsiveness. Furthermore, T3 supplementation until postnatal day 7 accelerated metabolic development by increasing pancreatic weight, islet cell density, and lowering fasting glucose levels, even with similar glucose tolerance test results. In contrast, T3 inhibition delayed pancreatic development. Additionally, a study in streptozotocin-induced diabetic rats showed that triiodothyronine could promote β-cell survival, reduce apoptosis, and improve glucose tolerance [8].

Thyroid hormone also directly stimulates pancreatic β-cells to secrete insulin and α-cells to release glucagon [6].

TH influences the gastrointestinal tract by enhancing glucose absorption through increased bowel motility [9]. An excess of thyroid hormone, or thyrotoxicosis, may induce a condition known as oxyhyperglycemia, characterized by a rapid increase in blood glucose following an oral glucose tolerance test (OGTT). Evidence suggests that this elevated glucose absorption results not only from increased gastrointestinal peristalsis but also from a direct T3-mediated enhancement of Na^+-glucose cotransporter (SGLT1) activity [10].

Thyroid hormone also affects the liver by increasing gluconeogenesis and glycogenolysis through stimulation of PEPCK transcription and activity—an enzyme that enhances gluconeogenesis [11]—thereby contributing to hyperinsulinemia and glucose intolerance [9].

Furthermore, TH enhances lipolysis in adipose tissue, resulting in increased circulating free fatty acids available for hepatic gluconeogenesis [12].

Thyroid hormone, particularly in hyperthyroidism, also affects skeletal muscles by upregulating the expression of glucose transporter type 4 (GLUT4) genes [9].

Thyroid hormone receptors (TRs) are expressed in both the human and rat hypothalamus, with abundant presence in the paraventricular (PVN) and arcuate nuclei

[13]. T3 has been shown to modulate hepatic glucose production via a central mechanism, independent of circulating glucoregulatory hormones and involving the sympathetic nervous system. In a clinical trial involving euthyroid rats, T3-sensitive neurons in the PVN were shown to induce endogenous glucose production through sympathetic projections to the liver [14].

A deficiency in thyroid hormone also affects glucose metabolism. Both clinical and subclinical hypothyroidism are associated with insulin resistance, while thyroid hormone supplementation and restoration of a euthyroid state are associated with improved insulin sensitivity [4, 5].

In contrast to thyrotoxicosis, hypothyroidism reduces glucose absorption from the gastrointestinal tract, delays peripheral glucose utilization, and decreases hepatic glucose output and gluconeogenesis. This decreased hepatic output helps to explain the lower insulin requirements in hypothyroid patients with diabetes and may compensate for peripheral insulin resistance. Importantly, reduced gluconeogenesis also accounts for the increased risk of hypoglycemic episodes in hypothyroid patients with type 1 diabetes [5].

Thyroid hormone deficiency also leads to reduced insulin sensitivity in skeletal muscle [15] and adipose tissue [16], resulting in diminished glucose disposal.

Supporting this, fludeoxyglucose uptake on PET imaging was found to be severely impaired in a hypothyroid patient with type A insulin resistance—a rare condition where insulin is largely ineffective due to severe tissue resistance—demonstrating the significant impact of hypothyroidism on glucose metabolism [5].

To maintain glucose homeostasis, pancreatic β-cells compensate for insulin resistance by increasing insulin secretion, resulting in chronic hyperinsulinemia—a central factor in the pathogenesis of type 2 diabetes [5, 17]. This deterioration of glucose metabolism leads to reduced glucose disposal and peripheral utilization, decreased metabolic clearance of glucose, and significantly lower insulin clearance rates.

2 Thyroid Disorders and Diabetes Mellitus

Dysthyroidism and diabetes often coexist: a 2010 meta-analysis of 10,920 patients with DM revealed an 11% prevalence of thyroid diseases in this population [18]. Perros et al. performed an annual screening for thyroid disease in a selected group of 1310 adult diabetic patients attending a diabetic outpatient clinic, reporting a 13.4% overall prevalence of dysthyroidism. They observed a higher rate in females with type 1 diabetes (31.4%) and a lower one in males with type 2 diabetes (6.9%). New thyroid diseases were diagnosed in 6.8% of the population screened [19].

2.1 Thyroid Disorders and T1D

Autoimmune thyroid disorders (AITDs) and type 1 diabetes (T1D) share a common autoimmune pathogenesis: AITD affects 17% to 30% of adults with T1D [20]. This association is primarily due to the presence of autoantibodies such as TPO-Ab and TG-Ab, which are the most common thyroid autoantibodies in patients with T1D (≈29%) [21].

AITD and T1D often co-occur in the same individual and among members of the same family. Both are chronic, multifactorial autoimmune endocrine diseases with overlapping etiologies. Several susceptibility genes, particularly those involved in T-cell activity (e.g., CTLA4, HLA class II, PTPN22, and IL-2Rα) [22], along with environmental factors, contribute to the development of both conditions [23].

In T1D patients, thyroid disorders may be asymptomatic or present with symptoms that are masked by poor glycemic control, leading to underdiagnosis and worsening of diabetic management. For this reason, many international guidelines—including those from the american thyroid association (ATA) [24], american diabetes association (ADA) [25], british thyroid association (BTA) [26], and american association of clinical endocrinology (AACE) [27]—recommend routine screening for thyroid disorders in children, adolescents, and adults with T1D.

2.2 Thyroid Disorders and T2D

Thyroid function is linked to insulin resistance not only in diabetic patients but also in individuals with normal glucose tolerance [17]. A higher prevalence of both hyperthyroidism and hypothyroidism is observed in the diabetic population. For example, the prevalence of hyperthyroidism among adults with T2D is approximately 4.4%, compared to 1.3% in the general U.S. population [19, 28].

Thyrotoxicosis can precipitate impaired fasting glucose and diabetes and can worsen glycemic control in patients with pre-existing T2D. In rare cases, it may trigger diabetic ketoacidosis in patients with T1D or T2D who have significant insulin deficiency [29].

Conversely, the prevalence of hypothyroidism in diabetic patients ranges between 5.7% and 25.3% [30, 31]. A meta-analysis showed that the risk of subclinical hypothyroidism is nearly twice as high in T2D patients compared to the general population. Moreover, lower FT4 levels are associated with higher HbA1c and poorer glycemic control [32].

Despite this, screening recommendations for thyroid dysfunction in T2D remain inconsistent. The ATA recommends at least a one-time TSH measurement in diabetic patients aged 35 years or older [24], whereas the USPSTF (United States Preventive Services Task Force) stated in 2015 that there was insufficient evidence to recommend routine thyroid screening in asymptomatic, nonpregnant adults [33].

2.3 Thyroid Disorders in Pregnant Women with Diabetes

During pregnancy, significant hormonal and metabolic changes affect both glucose homeostasis and thyroid function.

In healthy women and those with gestational diabetes, insulin sensitivity typically decreases by 50–60% to ensure adequate glucose supply to the fetus. This is compensated by increased insulin secretion. Gestational diabetes develops when pancreatic β-cell hypersecretion is insufficient to meet the increased demand [34].

Thyroid hormone production increases by about 50% during pregnancy, and the thyroid gland enlarges by 10–40% in iodine-deficient areas. WHO recommends an increased iodine intake during pregnancy (250 μg/day) [35].

In the first trimester, placental secretion of human chorionic gonadotropin (hCG), which shares an α-subunit with TSH, stimulates the thyroid, causing increased TH production and transiently decreased TSH levels. hCG is thus a physiologic stimulator of the thyroid and is largely responsible for transient, nonimmune hyperthyroidism in early pregnancy [35].

Diabetes mellitus (particularly gestational diabetes, GDM) and gestational dysthyroidism (GDT) are the most common endocrine disorders in pregnancy. Hypothyroidism, hyperthyroidism, and thyroiditis have respective prevalence rates of 2–3%, 0.1–0.4%, and 17% in the first trimester [36].

Women with GDM are at increased risk for hypothyroidism and postpartum thyroiditis. Notably, postpartum thyroiditis is three to four times more common in women with T1D [37].

This association may be attributed to insulin resistance induced by thyroid hormones or to placental abnormalities common to both GDM and GDT [38].

Clinical guidelines do not recommend universal screening for thyroid dysfunction in all pregnant women but rather target those with symptoms or belonging to high-risk groups (including patients with T1DM or a family history of thyroid disease). The ATA [35], BTA [26], and AACE [39] all recommend thyroid screening in pregnant women with T1DM.

2.4 Effects of Antidiabetic Agents on Thyroid Disorders

Evidence suggests that certain antidiabetic drugs in patients with type 2 diabetes may affect thyroid function.

Metformin administration in individuals with T2DM and primary hypothyroidism is associated with a reduction in TSH levels, without changes in plasma FT4 and FT3 concentrations. The TSH-lowering effect is detectable in both overt and subclinical hypothyroidism cases [40]. Furthermore, metformin has demonstrated antiproliferative effects against various types of cancer cells, including a potential reduction in thyroid nodule size and inhibition of thyroid cancer cell growth [41].

Sulfonylureas have been associated with antithyroid and goitrogenic activity [42]. Case-control studies report higher rates of hypothyroidism in patients treated with sulfonylureas compared to those managed with diet or insulin [43]. However, second-generation sulfonylureas appear to have a minimal impact on thyroid hormone metabolism [44].

Thiazolidinediones (TZDs), which are PPAR-γ agonists, act predominantly on adipose tissue but are also highly expressed in thyroid tissue—especially in patients with Graves' disease and in orbital tissue of individuals with thyroid eye disease (TED) [45]. Consequently, TZDs may exacerbate eye protrusion in patients with active TED and should be used with caution or avoided in such cases [46]. Conversely, a study on rosiglitazone suggested an inverse correlation with thyroid cancer risk [47].

Incretin mimetics, including GLP-1 receptor agonists, represent a newer class of antidiabetic drugs with significant impact on diabetes management. However, in vivo trials have shown some effects on thyroid cells. GLP-1 receptor agonists have been associated with C-cell proliferation and a potential increased risk of medullary thyroid carcinoma (MTC). Prolonged liraglutide use in rats has been shown to cause C-cell hyperplasia and calcitonin overproduction; however, these findings have not been replicated in monkeys or humans [48]. Although the FDA does not currently recommend routine MTC screening in patients on GLP-1 receptor agonists, their use is contraindicated in individuals with a personal or family history of MTC or multiple endocrine neoplasia type 2 (MEN2). Incretin mimetics may also influence TSH concentration, although this effect does not appear to be clinically significant [49].

Finally, SGLT-2 inhibitors represent another emerging area of interest in thyroid research. Current data on their effect on thyroid hormone metabolism remain limited and inconclusive, underscoring the need for further studies in this field [50].

3 Metabolic Basal Rate

The word metabolism (from Greek μεταβολή, meaning "change") refers to the set of life-sustaining chemical reactions—both anabolic and catabolic—that determine growth, renewal, and maintenance of an organism.

Thyroid hormones are key regulators of basal metabolism, which is closely linked to body weight regulation, obesity, and adiposity. Therefore, measuring basal metabolic rate (BMR) is essential for understanding and estimating energy balance and several metabolic disorders.

A comprehensive index of metabolism is the Total Energy Expenditure (TEE), which reflects the total amount of energy a person uses in a day. The major components of TEE include the following:

- *Resting Energy Expenditure (REE)*: First defined by Mitchell as the "minimum rate of energy expenditure compatible with life," REE refers to the energy

required to maintain essential physiological functions in a resting, awake state. It represents the largest component of TEE, accounting for approximately 60–80% in sedentary individuals [51]. REE can fluctuate depending on several internal and external factors, such as body composition, lean mass, hormonal status, and prolonged fasting [52].

- *Exercise Activity-Related Thermogenesis (EAT):* This includes energy expenditure from structured, voluntary physical activity. EAT is highly variable and influenced by body size, movement efficiency, and activity patterns. For example, a person might engage in 3 h of intense exercise 1 day and remain inactive the next, resulting in major day-to-day fluctuations.
- *Non-Exercise Activity-Related Thermogenesis (NEAT):* NEAT encompasses all physical activity not related to intentional exercise—such as walking to work, doing household chores, playing with children, or even fidgeting. NEAT can vary by up to 2000 kcal/day, depending on occupational demands and leisure activities [53]. For instance, individuals working in agriculture may expend up to 1500 kcal more per day due to high physical labor.
- *Thermic Effect of Food (TEF)*: TEF is defined as "the energy loss following food intake above and beyond the requirement for absorption, storage, and digestion." It usually constitutes about 8–15% of total daily energy expenditure. TEF can be influenced by dietary factors—larger meal sizes, high-protein intake, and low-fat plant-based diets are associated with increased TEF [54]. Furthermore, a randomized controlled trial demonstrated that insulin-stimulated increases in metabolic rate were greater in individuals without diabetes and progressively reduced in those with impaired glucose tolerance or diabetes. TEF also decreases with the progression of diabetes.
- *Adaptive Thermogenesis (AT):* AT refers to the energy converted into heat via mitochondrial oxidative phosphorylation uncoupling in brown and beige adipose tissue. Promoting adaptive thermogenesis is a promising strategy for obesity management, as it can enhance overall energy expenditure [55].

3.1 Major Methods to Measure Energy Expenditure

Metabolism functions as a cycle of bodily input and output. To assess energy expenditure (EE), one may measure either the intake—such as macronutrient or oxygen consumption—or the output, like heat production or carbon dioxide release. Although numerous efforts have been made to assess caloric intake, most have proven unreliable due to considerable underreporting, especially among individuals with higher BMI [56]. Consequently, research has shifted focus toward measuring energy expenditure, which can be accurately assessed through whole-room calorimeters, portable calorimeters, doubly labelled water, wearable devices, or (less accurately) personal logs [57].

Indirect calorimetry is currently the most accurate method for measuring EE. It is based on Weir's equation:

$$\mathrm{EE} = \left[3.94 \times \mathrm{VO}_2\right] + \left[1.1 \times \mathrm{VCO}_2\right],$$

where VO_2 is the volume of oxygen uptake and VCO_2 is carbon dioxide output. This technique estimates the calories consumed by an individual at rest by measuring the differential between inhaled and exhaled O_2 and CO_2 [58]. Furthermore, the ratio of CO_2 production to O_2 consumption allows the calculation of the respiratory quotient (RQ), which provides insight into substrate utilization—an RQ of 1 indicates carbohydrate oxidation, while 0.7 suggests predominant fat oxidation [59]. Given the close relationship between thyroid function and metabolic rate, indirect calorimetry has historically been the gold standard for assessing thyroid hormone activity in clinical settings.

The majority of indirect calorimetry tests are performed using the ventilated hood method, an open system that measures expired air while estimating inspired air through reference samples. This technique is relatively portable and cost-effective, and it can also be adapted to assess gas exchange during physical activity. However, limitations include the requirement for the subject to remain still, calm, and awake, and reduced accuracy due to the estimation (rather than direct measurement) of inspired air [60].

The whole-room calorimeter (or metabolic chamber) method involves continuous monitoring of the air entering and exiting a sealed room through a turbulent flow system. This allows for the assessment of energy expenditure over several days while the subject performs normal daily activities, including exercise [61, 62]. Currently, this is considered the gold standard for measuring total energy expenditure due to its high accuracy and capacity to measure all components of EE under near free-living conditions [1, 63]. Nonetheless, its disadvantages include high costs, the need for highly trained personnel, and limited ecological validity in replicating real-life conditions [2].

An alternative method involves doubly labelled water (DLW), where water containing stable isotopes is ingested and isotope elimination is tracked via mass spectrometry. This technique allows for the estimation of average TEE over a long period (typically 1 month) in free-living conditions. However, limitations include high costs, inability to separate EE components, and reliance on assumptions such as stable body weight and average dietary intake [2, 64].

Finally, accelerometers represent a noninvasive and low-cost alternative to estimate EE. Despite their appeal, these devices rely on multiple assumptions regarding movement and energy use, leading to lower overall accuracy [65].

3.2 Energy Expenditure and Diabetes Mellitus

Most studies examining basal metabolic rate (BMR) in individuals with diabetes mellitus (DM) report no significant difference in absolute resting energy expenditure (REE). This result may be due to the heterogeneity of the study populations.

However, after adjusting for age, sex, and fat-free mass, it appears that individuals with uncontrolled diabetes (HbA1c ≥ 8%) have a BEE (basal energy expenditure) that is 7.7% higher than that of healthy individuals. For example, a study conducted on Pima Indians demonstrated that REE, adjusted for body composition, sex, and age, was higher in subjects with type 2 diabetes (T2D) compared with the control group of nondiabetic individuals [66]. According to the authors, the increased EE could be explained by the higher energy demands of various organs (such as the lungs, heart, liver, and kidneys), which are likely to be exacerbated by increased fat mass. Additionally, more energy is required to carry and move a larger body, as individuals with T2D are more likely to suffer from obesity [67]. However, several potential modulators of energy expenditure were not assessed in this study, such as thyroid hormones [68], cytokines, and peptides (e.g., leptin, adiponectin, and tumor necrosis factor-α secreted by fat cells) [66, 69].

Furthermore, increased adiposity and insulin resistance are linked to hyperglycemia. Previous studies have suggested that higher blood glucose levels are associated with lower rates of weight gain, possibly due to increased energy expenditure (EE) [70, 71]. This hypothesis was supported by Piaggi et al. in 2015, whose study found that higher fasting plasma glucose after weight gain was associated with a greater-than-expected increase in EE. The rise in basal glucose output and insulin-induced suppression of EE at follow-up indicated that increased hepatic gluconeogenesis might be an important mediator of EE changes, alongside weight gain [71]. Thus, the higher BEE in patients with DM seems to be driven by increased fasting blood glucose, leading to higher glycosuria or gluconeogenesis. Hyperglycemia can increase glycosuria by 30–80 g/day, corresponding to an energy loss of approximately 120–320 kcal/day. Additionally, gluconeogenesis (an energy-consuming process that converts free fatty acids into glucose) accounts for approximately 29% of the variability in REE in adults with T2D [72].

In patients with decompensated DM, there is also intensified proteolysis (where protein breakdown exceeds protein synthesis) and altered sympathetic nervous system activity. Since muscle sympathetic nervous activity has been associated with total energy expenditure (TEE), this relationship may be influenced by hyperinsulinemia [73]. These factors may explain the body weight reduction that occurs in conjunction with poorly controlled diabetes. Evidence supporting this hypothesis comes from a randomized controlled trial (RCT) investigating the effect of insulin bolus on glucose and lactate. The study showed that both glucose and lactate concentrations declined in the following hour after the insulin bolus, along with a reduction in resting energy expenditure [74]. This study helped demonstrate that REE plays a key role in regulating body weight, and that REE, when normalized for fat-free mass, is significantly higher in diabetic patients—especially those with decompensated DM—before decreasing with improved glycemic control and insulin therapy [74].

Many studies have examined the relationship between diabetes and energy expenditure. One notable contribution was a case-control study that assessed resting metabolic rate (RMR) in patients with DM and obesity versus patients with obesity without DM. The results indicated that REE was significantly higher in the first

group (1480.7 ± 274.2 kcal/day vs. 1362.4 ± 184.8 kcal/day). Additionally, subjects with higher glycated hemoglobin (HbA1c) concentrations had higher REE than those with normal HbA1c levels [75].

3.3 Energy Expenditure and Obesity

The fundamental cause of obesity is a long-term energy imbalance, where too many calories are consumed and too few are expended. Evolutionarily, human beings are adapted to survive long periods of famine and undernutrition. As a result, in modern society, overeating, physical inactivity, and lower energy expenditure have become widespread phenomena [76]. Therefore, low energy expenditure can be considered a risk factor for weight gain and obesity. However, obesity is not necessarily linked to low energy expenditure. Many studies have shown that individuals with obesity often have greater amounts of both fat-free mass and fat mass compared to individuals with normal weight, along with increased resting energy expenditure (REE).

A case-control study has confirmed this by monitoring energy expenditure in 18 individuals with obesity compared to 23 individuals who had never been overweight. The results indicated that maintaining body weight at a level 10% or more below the initial weight was associated with a mean reduction in total energy expenditure (TEE) of 6 ± 3 kcal/kg of fat-free mass per day in the second group. In contrast, the first group showed an energy expenditure loss of 8 ± 5 kcal/kg/day [77].

It should also be noted that some individuals with obesity exhibit low resting energy expenditure and are classified as hypometabolic. This can be detected through appropriate investigation, such as indirect calorimetry. Mechanisms that could explain decreased REE in this group may involve mitochondrial dysfunction, mitochondrial degeneration, or downregulation of metabolic genes.

A promising therapeutic strategy for combating obesity is increasing the thermogenic capacity of adipose tissue to enhance energy expenditure. In particular, individuals with obesity seem to have higher expression levels of MKK6 (p38 MAPK activator) in white adipose tissue. In a clinical experiment in 2017 using knockout animals and shRNA, it was discovered that MKK6 deletion enhances energy expenditure and thermogenic capacity of white adipose tissue. This process also provides a protective role against diet-induced obesity and the development of diabetes mellitus in mice. Moreover, MKK6 deletion increases adipocytes' thermogenic capacity by enhancing T3-induced UCP1 expression. UCP1 uncoupling is a process through which brown and beige adipose tissues dissipate heat. MKK6 acts as a repressor of UCP1 expression, so its inhibition promotes adipose tissue browning and enhances energy expenditure. These results suggest that MKK6 not only regulates adipose tissue browning but also serves as a potential therapeutic target for reducing obesity [78].

3.4 Energy Expenditure and Thyroid Hormone

Thyroid hormone plays a crucial role in regulating energy expenditure. Its action is so pervasive that, as mentioned earlier, indirect calorimetry has historically represented the gold standard for the clinical assessment of thyroid hormone (TH) activity.

Thyroid hormone affects all components of energy expenditure (EE) and modulates them at the cellular level with several targets:

- Metabolic cycle: Promotes ATP utilization through processes such as lipolysis/lipogenesis, glycogenolysis/gluconeogenesis, phosphofructokinase/fructose 1,6-diphosphatase, hexokinase/glucose-6-phosphatase, protein synthesis, and catabolism.
- Ion leaks across the cell membrane: Most notably via the Na+/K+ ATPase and sarcoendoplasmic calcium ATPase.
- Oxygen consumption: By influencing the myocardium's inotropic and chronotropic actions.
- Mitochondrial respiration: By promoting mitochondrial biogenesis directly and stimulating the transcription of PGC-1α, the master regulator of aerobic respiration.
- Shunting of the proton gradient: In the inner mitochondrial membrane, diverting chemical energy into heat [79].

In short, thyroid hormone has pleiotropic effects on mitochondria and energy expenditure through direct actions on cellular respiration and ion channels.

3.5 Energy Expenditure and Hyperthyroidism

Untreated hyperthyroidism exemplifies the profound effects of thyroid hormone (TH) on energy expenditure (EE) so well that measurement of resting energy expenditure (REE) is often used to assess the severity of the disease [80].

In addition to its amplified effects on cellular respiration and thermogenesis, hyperthyroidism also affects the following systems:

- Cardiovascular system: Hyperthyroidism leads to an increase in resting heart rate, blood volume, myocardial contractility, and ejection fraction, which can result in high-output heart failure due to tachycardia-mediated cardiomyopathy [81].
- Sympathetic nervous system: This system is activated, generating fine tremors and an increase in spontaneous movements, which significantly increases nonexercise activity thermogenesis (NEAT) [82].
- Thermogenic brown adipose tissue (BAT): A major target of thyroid hormone, BAT can be directly stimulated through thyroid hormone receptors (TRs) expressed in brown adipocytes and indirectly through TRs expressed in

hypothalamic neurons. TH also induces the browning of white adipose tissue through both peripheral and central mechanisms.

Additionally, evidence suggests that thyrotoxicosis enhances a maladaptive activation of nonshivering thermogenesis in brown adipose tissue (BAT), further increasing EE [83]. This is likely due to an excess of circulating T3, rather than locally generated T3 from type 2 deiodinase (which is inhibited by circulating hormone). The excess T3 has positive transcriptional effects on UCP-1 in adipose tissue [84]. Moreover, increased glucose uptake in brown adipose tissue, mediated by T3's positive transcriptional effects on UCP-1, results in enhanced skeletal muscle metabolism and lipid oxidation rates.

A Korean trial investigated changes in basal metabolic rate (BMR) through indirect calorimetry in six women with Graves' disease, measuring EE at baseline and after 4, 8, 12, 26, and 52 weeks of treatment with methimazole. At baseline, BMR was 140% of predicted REE and progressively decreased over the weeks, reaching 113% at week 52. Free T3, free T4, and total T3 levels were significantly related to REE, as well as deiodinase activity [85, 86]. A trial on 21 Chinese women treated for hyperthyroidism found that EE was significantly reduced (28.7 ± 4.0 kcal/kg vs. 21.5 ± 6.1 kcal/kg), accompanied by a shift in substrate utilization from fat to carbohydrate oxidation. Changes in REE were linearly related to FT3 blood concentration, while leptin concentration showed no significant changes [87].

In addition to its effects on thermogenesis, lipid storage, and BMR, triiodothyronine (T3) influences appetite regulation through the central nervous system, primarily the hypothalamus [88]. Given these extensive effects, it is understandable why many researchers are focused on understanding and harnessing the role of TH in the treatment and amelioration of metabolic disorders such as obesity and diabetes [79].

3.6 Energy Expenditure and Hypothyroidism

Despite the dramatic impact of thyroid hormone on energy expenditure, it remains debated whether hypothyroidism could have a similar, but opposing, effect on basal metabolism, potentially leading to weight gain and obesity [89]. The ability to carefully regulate levothyroxine supplementation in patients who are partially or completely deficient in thyroid hormone has allowed, through monitoring endogenous thyroid hormone (TH) levels, the opportunity to study the correlation between hypothyroidism and energy expenditure.

A trial conducted on a small group of patients with hypothyroidism adjusted the levothyroxine dose to achieve a normal, slightly reduced, or slightly elevated TSH level. Results, measured in terms of resting energy expenditure (REE) using a ventilated hood, showed an inverse correlation between TSH and REE, with a change in REE of 15% as TSH ranged from 0.1 to 10 μUI/mL. Notably, free T4 levels never reached the normal range in all patients [90].

Studies using accelerometers and metabolic equivalent of task (MET) measurements did not observe any significant difference in REE. However, this is not surprising, given the limited sensitivity of these techniques [91].

A cross-sectional analysis involving 140 patients treated with levothyroxine replacement therapy similarly found no significant difference in REE between patients achieving low-normal TSH levels (<2.5 μUI/mL) and those with high-normal TSH levels (>2.5 μUI/mL). Conversely, free T3 was found to correlate directly with both energy expenditure and indices of adiposity, such as BMI, body composition, and fat-free mass (FFM). This observation confirms the link between thyroid hormone and adiposity [92].

A recent trial involving women with obesity and primary hypothyroidism, who were undergoing appropriate levothyroxine replacement therapy, showed that these women had lower REE compared to a control group (both for raw and adjusted data, considering age, BMI, body composition, and physical activity). Thus, hypothyroid women, despite having normal serum TSH levels, exhibited reduced REE. This finding supports the hypothesis that typical levothyroxine replacement therapy may not fully correct the metabolic alterations associated with hypothyroidism [93].

Collectively, available data suggest that changes in LT4 therapy, within the range commonly used in clinical practice, are not sufficient to induce a significant change in energy expenditure. However, it is clear that energy expenditure is directly related to triiodothyronine (T3) levels and may be inversely related to adiposity.

3.7 Syndrome of Resistance to TH and Energy Expenditure

The syndrome of resistance to thyroid hormone (RTH) is caused by inactivating mutations in the alpha or beta thyroid hormone (TH) receptor isoforms. While the alpha isoform has been recently recognized, the beta isoform is a well-known entity [94]. The selective expression of these isoforms helps to understand their different impacts on phenotype and energy expenditure.

Selective expression of the TH receptor beta isoform, which is located in the pituitary gland and liver, is associated with a shift in the TSH-TH correlation and a state of enhanced metabolism and higher energy expenditure due to tissues being overexposed to TH signaling [95]. Patients with this mutation may present with a wide range of clinical manifestations, from being asymptomatic to developing florid hyperthyroidism and a severe hypermetabolic state. In fact, resting energy expenditure (REE) can be 18% higher in patients with a beta isoform mutation compared to euthyroid subjects.

In contrast, RTH caused by mutations in the alpha isoform is linked to a hypometabolic state, due to the near-ubiquitous distribution of alpha receptors [96].

3.8 Functional Adaptation of TH Axis to Energy Expenditure

The thyroid hormone axis has been firmly recognized as a key regulator of energy expenditure (EE). However, evidence also suggests that the overall metabolic and energy status of the organism influences the TH axis, creating an afferent loop. In this way, the TH axis can be thought of as part of a larger network involving adipose tissue, the hypothalamus, the pituitary, and the thyroid. Leptin secretion from adipocytes stimulates the hypothalamus to release TRH, which then stimulates the pituitary gland to secrete TSH. TSH promotes the secretion of thyroid hormone and the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) [52].

The clinical correlation of these observations lies in the association between adiposity and serum T3 levels [97]. It is notable that this correlation is lost following weight reduction interventions. After weight loss, there is a marked decrease in T3 levels and energy expenditure (EE), which plays a significant role in the "metabolic memory" phenomenon. This, in turn, is a major driver of weight regain [98, 99].

Redman et al. demonstrated a 7% decrease in T3 levels after a 15% calorie restriction and subsequent weight loss [100]. Consequently, T3 replacement during weight loss interventions or its use at supraphysiologic doses to facilitate weight loss and prevent weight regain has been considered. However, such applications must be avoided due to their association with cardiovascular side effects [101].

Beyond its impact on basal metabolism, T3 also plays a regulatory role in the hypothalamus, where it regulates metabolism in the liver and brown adipose tissue (BAT) via both the sympathetic and parasympathetic branches of the nervous system:

- In the paraventricular nucleus, through sympathetic liver innervation, T3 regulates gluconeogenesis and hepatic insulin sensitivity.
- In the ventromedial nucleus, via the sympathetic nervous system, T3 induces BAT activation [52, 102].

4 Conclusion

Thyroid disorders and diabetes mellitus frequently coexist and are closely related. Thyroid hormones exert their pleiotropic effects by targeting multiple tissues, finely regulating energy metabolism, and maintaining the balance among energy intake, expenditure, and storage.

The clinical correlation between thyroid hormones and energy expenditure is well-documented, particularly in cases of overt hyperthyroidism and hypothyroidism. In fact, this correlation is so robust that it appears that standard levothyroxine replacement therapy may not fully correct the metabolic alterations associated with hypothyroidism. However, there is still ongoing debate as to whether mild or subclinical dysthyroidism impacts energy expenditure and body weight.

Similarly, diabetes mellitus—especially in its decompensated form—and obesity significantly influence energy expenditure. These conditions are often associated with higher resting energy expenditure (REE), which is not only due to the increased energy demands of organs and the additional energy required to move a larger body, but also due to mechanisms like increased glycosuria, gluconeogenesis, and proteolysis. However, the development of more specialized tools is necessary to assess energy expenditure more precisely in individuals with diabetes mellitus.

Questions for Self-Assessment

1. *What is the primary role of thyroid hormones in the body?*

   (a) To regulate immune responses
   (b) To control the production of red blood cells
   (c) To regulate energy expenditure and metabolism
   (d) To maintain heart rate and blood pressure

   Correct answer: (c) To regulate energy expenditure and metabolism
2. *Which condition is characterized by reduced thyroid hormone production and can result in a slower metabolism and weight gain?*

   (a) Hyperthyroidism
   (b) Hypothyroidism
   (c) Resistance to thyroid hormone
   (d) Obesity

   Correct answer: (b) Hypothyroidism
3. *In patients with hypothyroidism, what is often observed in terms of energy expenditure despite standard levothyroxine therapy?*

   (a) Increased resting energy expenditure (REE)
   (b) No change in resting energy expenditure (REE)
   (c) Decreased resting energy expenditure (REE)
   (d) Fluctuating energy expenditure without clear patterns

   Correct answer: (c) Decreased resting energy expenditure (REE)

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Further Reading/References

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New-Onset Graves' Disease and Type 1 Diabetes After COVID-19 and Anti-SARS-CoV-2 Vaccination

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Chapter Introduction: What You Will Learn in This Chapter
COVID-19 was shown to involve multiple extra-respiratory organs also leading to the occurrence of different autoimmune and endocrine pathological features. Several cases of newly diagnosed Graves' disease and type 1 diabetes after SARS-CoV-2 infection have been progressively described, and are mostly related to the disruptions of immune system typically present in COVID-19 patients and frequently triggering autoimmunity. Noteworthy, although anti-SARS-CoV-2 vaccinations have shown an excellent safety profile with very few adverse events reported, autoimmune disorders following vaccine administrations, also including Graves' disease and type 1 diabetes, have been consistently reported. These conditions were related to the potential occurrence of molecular mimicry processes or autoimmune syndromes induced by adjuvants triggered by the vaccine excipients. Interestingly, the postvaccination forms of Graves' disease have been characterized by distinctive different epidemiological pattern as compared to the wild-type forms reinforcing the potential causal association with vaccine administration. An early and prompt diagnosis of these conditions is recommended possibly including active surveillance with thyroid and glucometabolic functions in patients with persistent

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symptoms occurring after vaccination and in those with personal or familiar history of autoimmune diseases.

Learning Objectives

- COVID-19 was described as a pathological trigger for the new onset of autoimmune diseases mostly related to the disruptions of the immune system typically present during acute infection.
- Several cases of newly diagnosed Graves' disease and type 1 diabetes after SARS-CoV-2 infection have been progressively reported.
- The underlying pathophysiological mechanism of post-COVID-19 Graves' disease and type 1 diabetes is considered multifaced including viral-antigen molecular mimicry, cell-mediated immunity, and cytokine storm immune disruption.
- Although anti-COVID vaccinations have shown an excellent safety profile with very few adverse events reported, autoimmune disorders following vaccine administration have been consistently reported including the occurrence of Graves' disease and type 1 diabetes.
- These conditions were related to the potential occurrence of molecular mimicry processes or autoimmune syndromes induced by adjuvants triggered by the vaccine excipients.
- The postvaccination forms of Graves' disease have been characterized by distinctive different epidemiological pattern as compared to the wild-type forms reinforcing the potential causal association with vaccine administration.
- An early diagnosis of these conditions is recommended possibly including active surveillance with thyroid and glucometabolic functions in patients with persistent symptoms occurring after vaccination and in those with personal or familiar history of autoimmune diseases.

Definitions

COVID-19 Coronavirus disease 2019, SARS-CoV-2 severe acute respiratory syndrome-coronavirus-2, ACE-2 angiotensin-converting enzyme-2, TMPRSS2 transmembrane serine protease, GD Graves' disease, HT Hashimoto thyroiditis, GO Graves' ophthalmopathy, TRAb autoantibodies against TSH-receptor, T1D type 1 diabetes, ICA islet cell cytoplasmic antibodies, IAA insulin antibodies, GAD65 glutamic acid decarboxylase isoform 65 antibodies, IA-2 islet tyrosine phosphatase 2 antibodies, ZnT8 Zinc transporter isoform 8 antibodies, HLA human leukocyte antigen, DKA diabetic ketoacidosis, mRNA messenger RNA, AEFI Adverse events following immunization, ASIA autoimmune syndromes induced by adjuvants, PoVEO postvaccination early onset, TED thyroid eye disease.

1 COVID-19 and Related Endocrinopathies

Coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [1], has led to an impressive detrimental impact on global health system with 774 million affected cases and about 7

million of deaths [2]. COVID-19 severity widely differs ranging from mild fever and respiratory symptoms to severe forms with systemic and pulmonary irreversible complications and high risk of death [3].

SARS-CoV-2 has been firstly reported to primarily involve respiratory tract and lungs [3]. However, during the early pandemic spread, it was shown to involve multiple extra-respiratory organs also leading to the occurrence of several endocrine and metabolic pathological features [4–7]. The endocrine features firstly described mainly included disturbances in the hormonal hypothalamic-pituitary axis, thyroid and adrenal glands, glycemic status and calcium, vitamin D, and osteo-metabolic complications [8–15].

The most important cellular receptors used by SARS-CoV-2 for viral entry are the angiotensin-converting enzyme-2 (ACE-2) receptor and the coreceptor transmembrane serine protease (TMPRSS2) that are ubiquitously expressed in human tissues potentially explaining the broad tissue viral tropism. The presence of these receptors was also demonstrated in endocrine organs including thyroid, pancreas, testis, ovaries, and adrenal and pituitary gland, making these tissues potentially susceptible for a direct negative involvement by viral infection [5]. In addition, the pathophysiological mechanisms underlying the different endocrine alterations in COVID-19 patients were also related to the potential disruption of the immune system frequently triggering autoimmunity in these subjects. These autoimmune processes can occur both during the acute infections and after disease recovery, and are mostly related to dysfunction of cellular and humoral immune response, and to viral-self antigens molecular mimicry phenomena [16].

In this chapter, the COVID-19 and anti SARS-CoV-2 vaccination's negative autoimmune implications in thyroid gland and glucose metabolism, and their underlying potential pathophysiological mechanisms, will be presented and discussed.

2 COVID-19 and Autoimmunity

Autoimmune diseases are generally caused by a dysregulated activity of both adaptive and innate immune system self-targeting healthy tissues and organs. Although COVID-19 is mainly characterized by respiratory symptoms, it has also revealed complex interactions with human immune system with a causal pathophysiological key role in the occurrence and worsening of different autoimmune conditions [17].

Several underlying mechanisms have been progressively proposed for the occurrence of these specific COVID-19 complications. The first one is related to the molecular mimicry mechanism caused by the potential biological similarity observed between viral structural and functional components and different self-organ proteins and antigens. Indeed, different SARS-CoV-2 proteins were early proven to share considerable peptide-sequence similarities with human proteins, particularly in the sequence-region of the viral spike structures. This molecular mimicry is associated with antigens cross-reactivity leading to a subsequent immune activation of autoreactive lymphocytes and overproduction of autoantibodies

targeting self-antigens promoting the new-onset occurrence or worsening of previously present autoimmune processes [18]. The second mechanism is associated with the potential immune dysregulation caused by the hypersecretion of pro-inflammatory cytokines, chemokines, and other immune mediators during the acute cytokine storm typically observed in more severe patients. This uncontrolled hyper-inflammatory state is associated with an increased risk of immunological tolerance breakdown promoting the activation of autoreactive lymphocytes and leading to the occurrence of autoimmune responses [19]. Another proposed mechanism is regarding the potential viral tissue systemic persistence after the acute disease associated with a sustained low-grade chronic immune activation and epitopes spreading phenomenon possibly triggering the new onset of autoimmune responses during recovery [16], as previously observed also in Long COVID syndrome [20].

These hypotheses were progressively supported by robust clinical data reporting that COVID-19 was associated with the occurrence of several autoimmune conditions in previously healthy individuals including neurological, hematological, endocrine, and systemic autoimmune diseases [21–23].

A potential pathophysiological link associating COVID-19 with the occurrence of autoimmune conditions could be also identified in the widespread hypovitaminosis D consistently observed in COVID-19 patients [11, 24, 25]. The pleiotropic vitamin D hormone is known to be involved in the regulation of the immune response and immunocompetence [26] and, since the first pandemic spread, lower vitamin D levels were early described to characterize a distinctive osteo-metabolic phenotype present in COVID-19 patients [10, 14], and demonstrated to be independently associated with acute disease outcomes [27, 28], to influence antibody response to SARS-CoV-2 vaccines [29], and recently implicated also in the occurrence of Long COVID [20]. On the basis of the pleiotropic immunological effects of vitamin D hormone, in the last decades, the hypovitaminosis D has been also consistently suggested to predispose to the occurrence of different autoimmune diseases [26]. In this light, recently, the VITAL study, which included 25,871 participants, reported that supplementation with vitamin D for 5 years significantly reduced the risk of autoimmune disease by 22% as compared to placebo [30]. Therefore, since lower vitamin D levels have been reported to predispose both to COVID-19 occurrence and severity, and also to autoimmune thyroid and diabetic diseases [31, 32], a novel pathophysiological mechanism implicated in the occurrence of immune dysregulation in COVID-19 could be identified in the widespread hypovitaminosis D typically present in these subjects that may be associated with an increasing risk to develop autoimmune complications.

3 COVID-19 and the New Onset of Graves' Disease

The pathological spectrum of thyroid disorders occurred during and after SARS-CoV-2 infection widely ranges from subacute or painless thyroiditis to autoimmune thyroid disorders such as Graves' disease (GD) and Hashimoto thyroiditis (HT).

GD and HT are the most frequent autoimmune diseases affecting the thyroid gland. GD is the most frequent cause of hyperthyroidism, and it is associated with the presence of autoantibodies against TSH-receptor (TRAb), leading to a pathological hyperactivation of the thyroid gland on which we will focus our attention in this review [33]. Besides the underlying genetic and familiar predispositions, also different environmental factors are known to potentially contribute to the development of GD such as viral infections possibly leading to a dysregulation of both adaptive and innate immunity [34, 35].

Several cases of newly diagnosed GD and Graves' ophthalmopathy (GO) in patients previously affected by acute SARS-CoV-2 infection have been progressively described in literature [36–42].

The first report was published by Mateu-Salt et al. in 2020 reporting two cases of GD. The first patient, a 60-year-old woman, had a positive history of GD 30 years before and reported a GD relapse 1 month after SARS-CoV-2 infection. The second patient, a 53-year-old woman, had no history of previous thyroid disorder and developed GD 2 months after COVID-19 infection [36]. The second paper by Jimenez et al. in Spain reported two cases of GD concurrently diagnosed during acute SARS-CoV-2 infection. The first one was a 45-year-old female patient with a previous history of GD relapsing during the acute viral infection. The second one was a 61-year-old female patient presenting with atrial fibrillation due to the occurrence of a severe form of hyperthyroidism developed 1 month after COVID-19 [37]. Another case was reported in Boston by Feghali et al. in 2021 describing a 33-year-old female patient with no previous history of thyroid disorders that presented with palpitations and shortness of breath accompanied by worsening fatigue 2 months after COVID-19 infection. Biochemical examination was compatible with hyperthyroidism, along with elevated serum TRAb and high iodine uptake at thyroid scintigraphy [38]. A case of GD associated with GO was reported in Italy in 2021 in a 33-year-old female patient 2 months after COVID-19 infection [39]. In 2022, Ghareebain et al. described a 48-year-old male admitted to hospital for palpitations, fatigue and cough with no previous history of thyroid disorders who early developed GD after SARS-CoV-2 infection [40]. Two other cases of GD occurred 3-weeks after viral infection were reported in 2022, in a 22-year-old female patient and a 28-year-old-male patient, both without a previous history of thyroid disorders [41, 42].

A treatment with methimazole was started in all reported patients leading to an effective resolution of clinical symptoms and thyroid function normalization, without need of further therapies. Noteworthy, the time interval between the onset of GD and SARS-CoV-2 infection ranged from few days up to a maximum of 2 months after infection resolution. This short time interval consistently reported in most of reports strongly suggested the potential causal relationships between viral infections and GD occurrence. In addition, most of patients were not previously affected by thyroid disorders and this reinforces the potential putative key role of COVID-19 in the occurrence of GD.

To date, the underlying pathophysiological mechanism of post-COVID-19 GD is considered multifaced. Several potential hypotheses have been progressively proposed including viral-antigen molecular mimicry, cell-mediated immunity, and cytokine storm immune disruption [43].

The molecular mimicry hypothesis is supported by several studies describing a marked peptide sequence homology between SARS-CoV-2 and human proteins, in particular thyroid-derived peptides [44]. In fact, it was demonstrated that the main structural-proteins of SARS-CoV-2, such as the spike protein, the nucleoprotein, and the membrane protein, can potentially cross-react with thyroid peroxidase, a thyroid tissue protein, due to the biological similarity and homology of their peptide sequences [45]. In addition, it was also proven that thyroid parenchyma expresses a considerable concentration of ACE-2 receptors [46], leading thyroid cells potentially susceptible also to direct viral infection [47].

Therefore, the potential inflammatory and immune involvement of thyroid gland after SARS-CoV-2 infection was proposed to facilitate and promote the occurrence of specific autoimmune disorders including GD. On the basis of these potential pathophysiological mechanisms and the progressive increased reports of GD and other thyroid dysfunctions after COVID-19, a potential link between these two conditions, in specific patients, should be currently supposed [44, 45].

4 COVID-19 and New Onset of Type 1 Diabetes

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterized by the inflammatory damage of insulin-producing pancreatic beta-cells leading to an absolute insulin deficiency and consequent hyperglycemia and diabetes. Patients affected are typically characterized by the presence of specific autoantibodies including islet cell cytoplasmic antibodies (ICA), antibodies to insulin (IAA), glutamic acid decarboxylase isoform 65 (GAD65), islet tyrosine phosphatase 2 (IA-2), and Zinc transporter isoform 8 (ZnT8) [48]. T1D is one of the most frequent chronic diseases occurring in children with a worldwide incidence of 15 cases per 100.000 people and prevalence approximately around 5–10% of people with diabetes [49].

Although the specific pathophysiological mechanisms underlying the occurrence of T1D are still unknown, the genetic predisposition related to specific human leukocyte antigen (HLA) alleles and environmental factors seem to play crucial key roles [50]. A link between viral infections and new onset of T1D has been consistently reported in several studies for the past few decades assessing the link between rotavirus, enterovirus, mumps, measles and rubella virus, coxsackie virus and cytomegalovirus infections and T1D occurrence [51].

Regarding COVID-19 pandemic, type 1 and type 2 diabetes were early reported as relevant risk factors for COVID-19, whether if SARS-CoV-2 could be recognized as a putative causal agent of T1D still remains an open issue [52].

During the pandemic spread, several authors have reported a higher risk of developing T1D in COVID-19 patients [53]. A pediatric report showed an increase of 80% of newly diagnosed T1D in 2020 [54]. Later, a review by Rahmati et al. reported, after 1 year of pandemic spread, a worldwide increase in the incidence of pediatric T1D of 10%, diabetic ketoacidosis (DKA) of 25% and of severe DKA about 20% [55]. Moreover, data collected retrospectively from a national database

in the USA showed that COVID-19 diagnosis was associated with an increased risk of new-onset T1D particularly in specific ethnicities, such as American Indian/Alaskan natives and Asian or Pacific Islanders [56]. The authors also showed an increased risk of developing DKA in patients with pre-existing T1D after COVID-19 infection. However, population-based studies were not consistent in describing this proposed correlation between new onset of T1D and SARS-CoV-2 infection [57, 58]. In order to better characterize and analyze the epidemiological features and pathophysiological mechanisms of T1D cases after COVID-19, in 2020, Rubino and worldwide experts have established a global registry named CoviDIAB for patients with COVID-related diabetes, but no definitive data has yet been published [59].

A recent systematic review by Stathi et al. reported 37 cases of new-onset T1D related to SARS-CoV-2 infection, collected from 20 studies and published from 2020 to 2023 [60]. Twenty-three patients at the time of T1D diagnosis were concomitantly positive for SARS-CoV-2 testing, while the other 14 manifested the typical symptoms of COVID-19 or reported a previous recent (1 to 56 days before) positive SARS-CoV-2 testing. The occurrence of T1D after COVID-19 in male and female was similar, 54% and 46%, respectively. Patients' age ranged from 8 months to 33 years, with a higher prevalence (84%) of patients aged <17 years. Only 12 patients had a positive family history for type 1 or 2 diabetes and the most frequent comorbidities were obesity, celiac disease, and hypothyroidism with a prevalence of 2.5%, 1.3% and 1.3%, respectively. In most of patients, T1D occurred with typical symptoms including polyuria, polydipsia, polyphagia, fatigue or weight loss, and in most of them a form of DKA characterized by fever, weight loss, nausea/vomiting, abdominal pain and fatigue was present at diagnosis. All patients showed glycated hemoglobin levels >6.5% and blood glucose levels >250 mg/dL. The specific autoantibodies of T1D were measured only in 18 patients, of whom 13 had at least one positive result. Treatment in the acute setting consisted in intravenous fluids and insulin administration in all patients. Regarding the long-term treatment, all patients were managed with basal-bolus insulin therapeutic regimen and only one patient received also additional therapy with metformin.

Different potential mechanisms underlying the occurrence of T1D after SARS-CoV-2 infection were progressively proposed. It has been reported that the pancreatic beta cells express the SARS-CoV-2 entry receptor ACE-2 and neuropilin-1 on their cell surfaces, and different studies have confirmed that beta cells can be specifically infected by SARS-CoV-2 [61]. Moreover, the ACE-2 receptor expression on pancreatic beta cells was reported to be stimulated by cytokines activation during acute COVID-19 which, in turn, could increase the viral infection susceptibility [62]. The beta cells destruction could be related both to the cytopathic direct damage caused by virus entry and replication, and also to the activation of natural killer cells though antibody cell-mediated cytotoxicity in the presence of anti-SARS-CoV-2 autoantibodies [63]. In addition, also molecular mimicry and epitope spreading were proposed to be involved in the virus-induced beta cell dysfunction and autoimmunity triggering.

The temporal associations between T1D diagnosis and COVID-19 occurrence reported in most of studies initially suggested a causal relationship between these two conditions. However, since glycated hemoglobin levels were increased in all patients, and that most of them were positive at SARS-CoV-2 diagnostic tests before or concomitantly with the hospitalization, it seems that the viral infection could likely act more as a precipitating risk factor for T1D development rather than being the direct causative phenomenon of this condition. Therefore, further conclusive data derived from larger cohort and prospective studies, in addition to epidemiological worldwide data, are needed to better define the link between COVID-19 and development of T1D and explaining this potential association.

5 Anti-SARS-CoV-2 Vaccination and Autoimmune Disorders

By the end of 2020, vaccines against SARS-CoV-2 have been used to reduce the worldwide clinical impact of acute COVID-19. For the first time, vaccines based on messenger RNA (mRNA) technology (Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273) have been used for an infectious disease [64]. To date, 12 different vaccines have been granted an emergency use approved by the World Health Organization and administered worldwide also including viral vector vaccines (Vaxzevria ChAdOx1, AstraZeneca and Janssen Biotech) and inactivated virus vaccines [65]. Nowadays, worldwide, 13 billion people have been vaccinated against SARS-CoV-2 and vaccines have dramatically reduced COVID-19 mortality [66].

These vaccines have shown an excellent safety profile with very few adverse events reported. Adverse events following immunization (AEFI) refer to any medical occurrence following immunization including a wide spectrum of adverse reactions. The most frequent AEFI are characterized by mild symptoms such as local injection site reactions and systemic manifestations (fever, fatigue, nausea, headache, myalgia, arthralgia, dizziness); however, less frequently, life-threatening conditions such as anaphylactic and hypersensitivity reactions (respiratory complications, wheezing, swelling of the throat) have also been reported. Another rare but serious adverse event associated with adenoviral vector-based anti-SARS-CoV-2 vaccines was the thrombosis with thrombocytopenia syndrome, a hematological condition characterized by multiple systemic blood clotting combined with low platelet count [67]. Of note, also a slight significant increase in the risk of self-limited myocarditis and pericarditis have been reported in young males following Pfizer/BioNTech and Moderna anti-SARS-CoV-2 vaccinations [68].

Interestingly, also autoimmune disorders following anti-SARS-CoV-2 vaccinations have been consistently reported including autoimmune hepatitis [69], myocarditis and myopericarditis [70], Bell's palsy and Guillain–Barre syndrome [71], thrombotic thrombocytopenia [72], renal minimal change disease, and endocrine autoimmune manifestations [73].

Multiple pathophysiological mechanisms have been proposed for anti-SARS-CoV-2 vaccine-induced autoimmunity, involving interactions among genetic predisposition, environmental factors, and dysregulated immune response. As discussed above, also in this setting the molecular mimicry processes, related to the biological similarity between self-antigens and viral vaccine proteins, may play a key role [44]. On the other hand, in the trigger of autoimmune disorders related to vaccination, a specific role could be represented by the vaccine adjuvants. The adjuvants are different protein- or lipids-based components added to vaccines structurally or functionally which are required to guarantee vaccine action and efficacy. Pfizer/BioNTech and Moderna vaccines are mRNA-based vaccines transporting viral spike protein genetic information that use lipid nanoparticles, useful to stabilize and facilitate mRNA transport into cells, such as polyethylene glycol lipids [74, 75] that were previously associated with the occurrence, in predisposed individuals, of autoimmune, autoinflammatory, and anaphylactic responses [76–80]. The list of excipients contained in Vaxzevria ChAdOx1 vaccine, based on an inactivated modified viral vector technology with a nonreplicating recombinant adenovirus, includes polysorbate 80, an oil-in-water emulsion excipient, that was previously reported to be associated with autoimmune and autoinflammatory responses [81–83]. The syndromes potentially related to the vaccine-adjuvants injection are called as autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [84]. ASIA are known to include various autoimmune diseases affecting collagen, neurological, hematological, hepatic, and also endocrine disorders including subacute thyroiditis, HT and GD.

5.1 Anti-SARS-CoV-2 Vaccination and New Onset of Graves' Disease

In the first few months since the beginning of anti-SARS-CoV-2 vaccination use worldwide, the occurrence of thyroid disorders after vaccine injections was early described in literature as a potential side effect, most of them reporting cases of subacute thyroiditis [85] and GD [73, 86].

To date, two main hypotheses have been proposed as underlying pathophysiological mechanisms of GD occurrence following anti-SARS-CoV-2 vaccination: molecular mimicry involving viral structural and thyroid peroxidase proteins, and ASIA syndrome [84, 87].

The first cases of GD after vaccinations were reported in three female patients and only one male patient prevalently in young-adult age [88, 89], reflecting the typical epidemiological age and sex distribution of the sporadically occurred disease and therefore without excluding the presence of only a casual relationship between vaccinations and occurrence of these forms of GD [90]. However, di Filippo et al. have subsequently reported the occurrence of GD specifically in two male patients after Vaxzevria anti-SARS-CoV-2 vaccinations, strengthening the

hypothesis of a causal vaccine-GD relationship, since males are more rarely affected by GD and less susceptible to develop autoimmune syndromes [91].

To better characterize the occurrence of GD after vaccination, in 2021, di Filippo et al. described a new entity of postvaccination early-onset (PoVEO) GD after anti-SARS-CoV-2 vaccines in an Italian tertiary level hospital [92]. They collected clinical information during the entire period of 2021 and described 64 patients with new diagnosis of GD. Twenty patients developed GD within 4 weeks after vaccination, while 35 and 9 patients developed GD before vaccination and more than 8 weeks after vaccination, respectively. This study reported that patients with early-onset GD were more likely to be males and of older age compared with the other two groups, highlighting in this group of patients a different epidemiological pattern as compared to wild-type GD mainly affecting, on the contrary, younger and female subjects. Three months after starting therapy with methimazole, those with PoVEO GD presented lower levels of TRAb titer and were taking lower doses of methimazole therapy as compared to the other patients. This relatively large series suggests that in 2021, PoVEO GD was a new nosologic entity representing one-third of patients evaluated for new-onset GD in a tertiary center with distinctive features including older age at onset, higher male prevalence, and a better initial biochemical and immunologic response to treatment. These distinctive features, different as compared to those observed in the sporadically occurring GD cases, reinforced the hypotheses of potential casual associations between vaccination and PoVEO GD occurrence (Fig. 1). In a recent Japanese review by Takedani et al., 62 cases of GD have been described after administration of five different types of vaccine [93]. All patients showed positive TRAb, male prevalence reached 30% (approximately 3 times higher than male prevalence in wild-type GD), and the median symptoms time onset after vaccination was 17.7 days. All patients were treated with methimazole and showed a rapid good clinical and biochemical response, confirming the first data reported by di Filippo et al. New onset of thyroid eye disease (TED) after mRNA vaccines have been also reported. A recent review of the literature described 10 cases of TED [94]. Among them, only two patients had no previous history of autoimmune thyroid diseases, while 6 were previously affected by GD and two by HT diseases. All patients were characterized by the presence of higher TRAb and typical signs and symptoms of GO with mild-to-moderate severity clinical activity scores. In a recent review by Chen et al. published in 2023, 62 cases of GD after vaccination were described [95]. Forty-seven GD cases were new-onset disorders, of which 33 after mRNA vaccines and 14 after viral vector vaccines, while 15 cases were relapse of previous diseases, 10 after mRNA vaccines, 4 after viral vector, and 1 after inactivated vaccines. The mean age of patients affected was 43 years with a 27% male prevalence. The median symptom onset time after vaccination was 12 days and the median symptoms duration was longer in relapsed cases than new-onset GD. Clinical manifestations of new-onset diseases were similar to the relapsing GD, although in 5 new-onset cases, the patients affected did not report thyrotoxicosis symptoms and the diagnosis was incidentally performed.

Importantly, in all these reports, the authors suggest that in those with a new-onset GD after vaccination, the further vaccine doses should be temporarily avoided

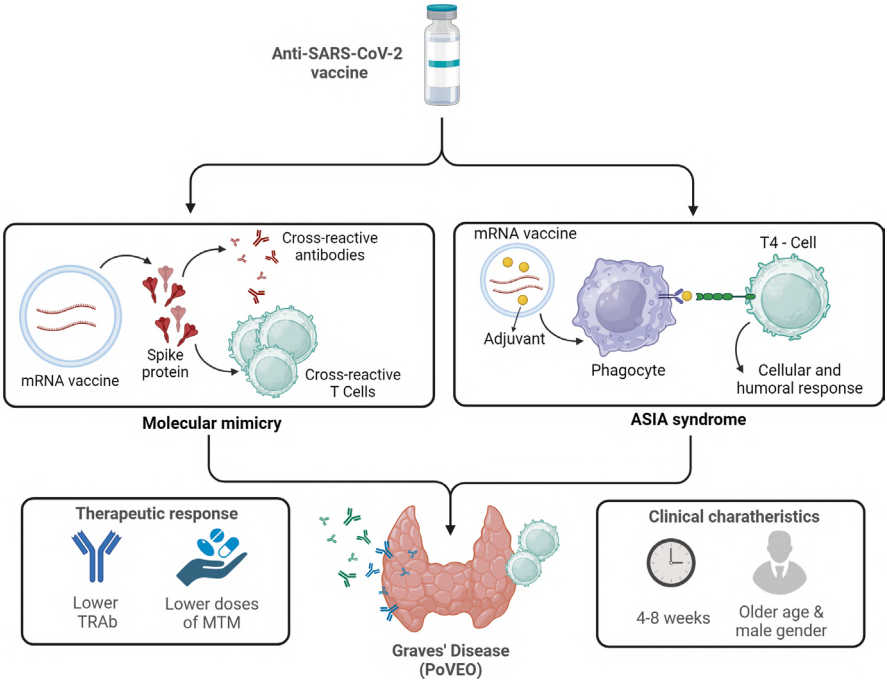

Fig. 1 Pathophysiological mechanisms underlying the postvaccination early-onset (PoVEO) Graves' disease after anti-SARS-CoV-2 vaccines. *Abbreviations*: mRNA messenger RNA; ASIA autoimmune syndrome induced by adjuvants; MTM: methimazole; PoVEO: postvaccination early onset; TRAb: autoantibodies against TSH-receptor

and administered only after normalization of thyroid function in order to avoid the potential risks of worsening of thyrotoxicosis.

5.2 Anti-SARS-CoV-2 Vaccination and New Onset of Type 1 Diabetes

Presence of diabetes is considered one of the worst risk factors for negative clinical outcomes in COVID-19 patients and, therefore, vaccination against SARS-CoV-2 was strongly and early recommended in diabetic subjects.

A recent meta-analysis reported no significant changes of glycometabolic parameters (glucose time in range and time above range) in 632 T1D patients after first and second dose of vaccinations, including all types of vaccination [96]. On the other hand, some authors reported worsening glycometabolic state in patients with type 2 diabetes after administration of the first dose of ChAdOx1 nCoV-19 vaccine, also presenting cases of new-onset hyperosmolar hyperglycemic state (HHS) [97, 98].

As reported above for GD after vaccinations, different studies have progressively highlighted possible relationships also between vaccinations and T1D occurrence, potentially caused by the previously discussed pathophysiological mechanisms including altered immune response hyperactivity, ASIA syndrome, and lymphocytes activation by molecular mimicry processes.

Yakou et al. in 2021 reported the first case reports of acute DKA in two T1D patients after anti-SARS-CoV-2 vaccination [99]. In the first case, a 71-year-old woman developed immediate symptoms after receiving the first dose of Pfizer/BioNTech vaccine. The second patient, a 47-year-old woman, developed nausea, palpitation, and respiratory distress after the second dose of Pfizer/BioNTech vaccine. Subsequently, other case reports of fulminant T1D clinically presenting with DKA and occurring after anti-SARS-CoV-2 vaccinations were reported in literature [100–104]. Management was performed in all patients with intravenous fluid and insulin administration.

A recent review by Alsudasi et al., published in 2023, reported 12 cases of new-onset T1D after anti-SARS-CoV-2 vaccination from 8 different studies [105]. Interestingly, and as previously discussed also for GD after vaccinations, median age of patients affected was 49 years, older as compared to that typically observed in those presenting with sporadically occurred T1D. Fifty-eight percent was female, and 25% of patients had a previous history of autoimmune disease. mRNA vaccines were administered in 10 patients (83%). Mean time of symptoms occurrence after vaccinations varied from 3 days to 8 weeks, and clinically DKA was reported in 41% of cases. In most of patients, biochemical evaluation showed the presence of T1D autoantibodies, low to undetectable levels of c-peptide, and a high prevalence of HLA-DQB1 polymorphisms. Noteworthy, two patients had a positive history of type 2 diabetes mellitus for more than 7 years, and one was characterized by a status of prediabetes before the vaccination. Except the history of autoimmune diseases and genetic susceptibility, no other specific risk factors were identified for the occurrence of these cases.

Interestingly, a case report of a 52-year-old woman concomitantly developing both GD and T1D following anti-SARS-CoV-2 vaccination was also recently described [106]. The patient clinically presented with fever, weight loss, and asthenia 4 weeks after the second administration of Pfizer/BioNTech anti-SARS-CoV-2 vaccine. An acute DKA with biochemical presence of GAD-positive autoantibodies was diagnosed. In addition, she presented thyroid goiter at clinical evaluation and biochemical thyrotoxicosis along with increased TRAb levels. The patient was treated with methimazole and insulin therapy reporting a progressive improvement of symptoms and of thyroid function and glycemic control. This peculiar clinical report can reinforce the hypothesis that vaccination can have, in some specific cases, a potential causal key role in the occurrence of these two autoimmune endocrine disorders.

6 Conclusions

Besides the detrimental respiratory involvement, SARS-CoV-2 was also early described as a potential pathological trigger for the new onset of autoimmune endocrine diseases, in particular GD and T1D, through different hypothesized mechanisms of immune disruption and molecular mimicry. On the other hand, even though different anti-SARS-CoV-2 vaccines were developed and were found to be highly effective in reducing the COVID-19 spread and mortality, they had their own side effects, namely, potential triggers of immune-mediated adverse events, including new-onset GD and T1D with peculiar different characteristics as compared to the sporadically occurred forms, reinforcing the potential causal associations between the occurrence of these autoimmune disorders and vaccinations.

An early and prompt diagnosis of GD after anti-SARS-CoV-2 vaccination and increased medical awareness about this possible complication should be managed, also recommending to include an active surveillance with thyroid function monitoring in patients with marked and persistent symptoms occurring after vaccination potentially overlapping to those present during thyrotoxicosis such as fever and palpitations. This should be recommended with particular attention in patients with personal or familiar history of autoimmune thyroid and nonthyroidal diseases, and in adult male population generally not affected by the sporadically occurred GD forms. Patients affected by post-anti-SARS-CoV-2 vaccination GD showed a good initial response to medical treatment and, therefore, a temporary postponement of further vaccine doses after the complete restoration of thyroid function could be cautiously recommended to avoid worsening of thyrotoxicosis. Anti-SARS-CoV-2 vaccination remains strongly recommended in all diabetic patients, especially in children with T1D. However, it should be also important to perform a glycometabolic biochemical surveillance screening and to improve an active education regarding the possible postvaccination adverse events in all patients with T1D, prediabetics, or with a positive family history for diabetes.

Questions for Self-Assessment

1. *Which of the following is a proposed mechanism linking SARS-CoV-2 infection or vaccination to the onset of autoimmune diseases such as Graves' disease and type 1 diabetes?*

   (a) Direct viral cytotoxicity to immune cells.
   (b) Molecular mimicry and immune system hyperactivation.
   (c) Increased insulin sensitivity.
   (d) Decreased cytokine production.

   Correct answer: (b) Molecular mimicry and immune system hyperactivation

2. *In the reported cases, what temporal relationship was commonly observed between SARS-CoV-2 vaccination and the onset of autoimmune diseases like Graves' disease and type 1 diabetes?*

   (a) Symptoms always occurred within 6 hours of vaccination.
   (b) Autoimmunity typically developed years after vaccination.
   (c) Autoimmune manifestations appeared within days to a few weeks post vaccination.
   (d) There was no consistent temporal pattern.

   Correct answer: (c) Autoimmune manifestations appeared within days to a few weeks post vaccination.

3. *What is the current stance of the scientific community regarding the link between COVID-19 vaccination and autoimmune diseases such as Graves' disease and type 1 diabetes?*

   (a) A definitive causal relationship has been established.
   (b) The link has been entirely ruled out by large-scale studies.
   (c) There is a hypothesized association requiring further investigation.
   (d) Vaccination is contraindicated in patients with autoimmune predisposition.

   Correct answer: (c) There is a hypothesized association requiring further investigation.

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Fractures in the Elderly with Osteoporosis

F. Ramella, P. Fici, and P. S. Randelli

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Chapter Introduction: What You Will Learn in This Chapter

In this chapter, we explore the diagnosis and treatment of proximal humerus fractures, which are complex injuries commonly encountered in orthopedic practice. Proximal humerus fractures are often multifragmentary and can be displaced, requiring a precise approach to diagnosis and careful consideration in the choice of treatment. Understanding these fractures' diagnostic imaging and treatment protocols is critical for effective patient management.

This chapter connects with other chapters in the book that focus on musculoskeletal injuries and treatment strategies, providing readers with insights into both conservative and surgical management. By understanding the diagnostic methods, treatment options, and outcomes, clinicians will be better equipped to handle a range of proximal humerus fracture cases in clinical practice.

Key points covered in this chapter include the following:

- Diagnostic imaging techniques for proximal humerus fractures.
- Indications for surgical and nonsurgical treatments.
- Management strategies for both simple and complex fractures.
- The importance of patient factors in deciding treatment approaches.

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Learning Objectives
By the end of this chapter, readers should be able to:

1. Understand the diagnostic imaging methods used to evaluate proximal humerus fractures, including radiography and CT scans.
2. Differentiate between absolute and relative indications for surgical treatment of proximal humerus fractures.
3. Apply knowledge of fracture types and treatment options to clinical decision-making.
4. Recognize the impact of patient age and comorbidities on treatment choices for these fractures.

Definitions
Before diving into the clinical details, it is important to define several key terms that will be frequently used throughout this chapter:

- Proximal Humerus Fracture: A break in the upper part of the humerus (upper arm bone), which may involve the humeral head, surgical neck, or greater/lesser tuberosities.
- Comminuted Fracture: A type of fracture where the bone breaks into multiple fragments.
- Displaced Fracture: A fracture where the bone fragments are no longer aligned and have shifted out of position.
- Avascular Necrosis (AVN): The death of bone tissue due to a lack of blood supply, often a concern in fractures involving the humeral head.
- Intramedullary Nail: A metal rod inserted into the bone's marrow canal to stabilize fractures, often used for surgical neck fractures.
- Prosthetic Replacement: A surgical option involving the implantation of a shoulder prosthesis (either anatomic or reverse) for complex fractures.

1 Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by reduced bone mass and qualitative skeletal alterations (macroarchitecture and microarchitecture, material properties, geometry, microdamage) that lead to increased bone fragility and fracture risk [1–3]. It can be classified into two forms [3]:

1. Primary Osteoporosis: No predominant risk factors are identifiable. This form can be postmenopausal or senile.
2. Secondary Osteoporosis: Caused by a well-defined etiological factor, like certain health conditions, medications, or lifestyle factors. These factors can interfere with bone density and contribute to bone loss, leading to secondary osteoporosis.

(a) Endocrine or hormonal imbalance conditions:

(i) Hyperthyroidism.
(ii) Hypogonadism.
(iii) Cushing's syndrome.
(iv) Type 1 diabetes.

(b) Chronic kidney or liver diseases.
(c) Chronic inflammatory conditions:

(i) Rheumatoid arthritis.
(ii) Cystic fibrosis.

(d) Eating disorders: Anorexia nervosa

Osteoporosis can go undetected for years until a fracture occurs. Osteoporotic or fragility fractures are caused by traumas that are, by definition, insufficient. This means that the energy involved is equal to or less than that from a fall in an upright position. Falls are the most common cause of fractures in the appendicular skeleton. In contrast, osteoporotic vertebral fractures are called "vertebral sagging," because the vertebral bodies are so fragile that they collapse upon themselves until they assume a flattened shape ("vertebra plana").

Fractures due to osteoporosis or fragility can affect all bones in the body except for the skull. They tend to occur more frequently in bones where cancellous bone tissue predominates. Cancellous bone is more metabolically active due to its greater vascularity compared to cortical bone, making it more sensitive to metabolic changes in the body. These changes include those associated with osteoporosis.

The preferred sites for these fractures include the following [4]:

- Proximal femur.
- Vertebral bodies.
- Distal radius.
- Proximal humerus.
- Pelvis.

These fractures represent a burden in the lives of those who endure them. Osteoporotic patients often have various comorbidities, and fractures contribute to complex disability and reduced quality of life due to functional limitations [2, 3].

2 Epidemiology

A systematic review and meta-analysis based on WHO diagnostic criteria in 2022 estimated the global prevalence of osteoporosis to be between 19.7% and 21.7%. There is significant variation across countries (from 4.1% in the Netherlands to 52% in Turkey) and continents (8% in Oceania, 26.9% in Africa). Additionally, osteoporosis is more prevalent in developing countries (22.1%) compared to developed countries (14.5%) [2, 5].

In Italy, according to ISTAT data from 2020, osteoporosis affects five million people (8.1% of the total population), with 80% of cases occurring in postmenopausal women. Prevalence increases with age, reaching 32.2% in individuals aged 75 and older [6].

Globally, there are approximately 8.9 million osteoporotic fractures each year. They occur at a rate of one fracture every 3 seconds, affecting 1 in 3 women and 1 in 5 men over the age of 50. In the United States, about 1.5 million fragility fractures occur annually, while in Europe, the number is approximately 4.3 million [2].

Because of the ageing of the population all over the world, it is estimated that the number of osteoporotic fractures will increase by approximately 25% over the next 10–15 years.

From a distribution perspective, there is a higher incidence of proximal femur fractures in Europe (particularly in Northern Europe), while the lowest percentage has been registered in East Asia [4]. The origins of these differences are not clear from a scientific standpoint and cannot be solely attributed to differences in bone mineral density [7, 8].

The high prevalence of fragility fractures and their associated complication is one of the most significant financial burdens on healthcare systems worldwide. These fractures represent a public health problem in all countries.

In Europe and North America, the prevalence, prognosis, and financial burden associated with this type of fracture can be comparable or even greater in some cases than those of cardiovascular diseases. Overall, it is estimated that they cost healthcare systems 56 billion euros annually. Specifically, in the United States, the estimated cost is 5–10 billion dollars per year [1, 2, 9].

Given these factors, it is increasingly imperative to implement fracture prevention strategies, including targeted screening for at-risk populations, early treatment of osteoporosis, and reducing the incidence of these conditions.

3 Risk Factors

The pathogenesis of fragility fractures must consider multiple factors that can influence both bone strength and the frequency and type of resulting injuries. The risk of experiencing these fractures is determined by a combination of factors that act through a reduction in Bone Mineral Density (BMD) and factors that are partially or entirely independent of BMD.

The most common risk factors include the following:

- Age.
- Smoking.
- Family history of fragility fractures.

- Previous fractures.
- Reduced BMD.
- Immobility.
- Comorbidities (such as diabetes, chronic kidney disease, and altered calcium metabolism).
- Fall risk factors (such as senile dementia, Alzheimer's disease, Parkinson's disease, and gait disorders).

Some of these risk factors are not modifiable, such as age, family history of fragility fractures, and previous fractures. However, for other factors, strategies can be implemented to reduce their impact on bone health. These strategies may include smoking cessation, regular bone health screenings using radiographic and laboratory diagnostic tests, optimal management of comorbidities to maintain parameters within acceptable ranges and creating protected and controlled environments for elderly patients at high risk of falls.

4 Diagnosis and Risk Assessment

The diagnosis of osteoporosis and the assessment of fragility fracture risk require a comprehensive approach to the patient, based on various evaluation methods:

4.1 Medical History (Anamnesis)

Collecting the patient's medical history is essential to identify potential risk factors. Key information for suspected osteoporosis includes the following:

- Previous fragility fractures.
- Family history of fractures.
- Comorbidities.
- Medications.
- Gynecological history and age at menopause.

4.2 Physical Examination (Objective Assessment)

A thorough physical evaluation can reveal signs of bone fragility, such as posture, height, and possible deformities. The development of kyphosis (excessive curvature of the spine) or loss of height may be related to one or more vertebral collapses.

Table 1 First- and second-level laboratory tests for the diagnosis of osteoporosis

First-level laboratory tests	Second-level laboratory tests
Erythrocyte sedimentation rate (ESR)	Ionized calcium
Complete blood count	Thyroid stimulating hormone (TSH)
Protein electrophoresis	Parathyroid stimulating hormone (PTH)
Calcemia	25-OH-vitamin D
Phosphoremia	Blood cortisol after overnight suppression test
Total alkaline phosphatase	Free androgen index
Blood creatinine content	Blood and urinary immunofixation
24 h Calciuria	Anti-transglutaminase antibodies

4.3 Laboratory Tests

First- and second-level laboratory tests can provide valuable information about the patient's bone health. First-level tests are less specific and may include markers of inflammation, complete blood count, electrolytes, and protein evaluation. Second-level tests are more targeted and focus on hormones that influence bone metabolism or specific tests for associated pathologies (see Table 1).

4.4 Instrumental Examinations

- Dual-Energy X-ray Absorptiometry (DXA): DXA, previously known as DEXA or MOC, is a radiological examination characterized by an extremely low radiation dose (approximately 0.001 mSv, one-hundredth of that from a standard chest X-ray). It is based on the principle of attenuation, where the targeted segment is irradiated with two X-ray beams of different energy levels. This allows differentiation between hard and soft tissues. By excluding soft tissues from the examination, bone density can be evaluated.
- Bone Ultrasonography: This technique assesses bone health using ultrasound waves.
- Conventional Radiology: Standard X-rays are commonly used to evaluate bone density and identify any fractures.
- Spinal MRI (Magnetic Resonance Imaging) and CT (Computed Tomography): These diagnostic tools are essential for assessing bone mineral density and detecting potential fractures.

According to the World Health Organization (WHO), assessing BMD using DXA is the gold standard for diagnosing osteoporosis [1, 10, 11]. Diagnostic thresholds, established in 1994, are based on the difference in standard deviations between a patient's BMD and that of a reference population of young adults (T-score) [12]. Here's how T-scores are interpreted:

- T-score greater than −1.0: Falls within the physiological range of bone health.

- T-score between −1.0 and −2.5: Classified as osteopenia (lower bone density).
- T-score less than −2.5: Diagnosis of osteoporosis or severe osteoporosis if associated with any fragility fracture.

However, relying solely on BMD as a clinical indicator of fracture risk has limitations. Many fragility fractures occur in individuals with BMD values above the threshold. Therefore, additional clinical risk factors, independent of BMD, play a crucial role in assessing fracture risk [4].

Several easily identifiable clinical risk factors, such as age, sex, and previous fractures, can be used for fracture risk evaluation, either with or without BMD assessment. To enhance risk prediction, noninstrumental tools, including questionnaires, have been developed. These tools estimate absolute fracture risk by combining clinical risk factors with diagnostic and laboratory examinations. The *FRAX (Fracture Risk Assessment Tool)* is the most extensively studied tool for assessing fracture risk. It has been incorporated into over a hundred different clinical practice guidelines. FRAX estimates the ten-year probability of overall osteoporotic fracture and specifically proximal femur (hip) fracture.

The items requested by the questionnaire to calculate the ten years probability of fracture are listed as follows:

1. Age.
2. Sex.
3. Weight (kg).
4. Height (cm).
5. Previous fracture (YES/NO).
6. Parent fractured hip (YES/NO).
7. Current smoking (YES/NO).
8. Glucocorticoids (YES/NO).
9. Rheumatoid arthritis (YES/NO).
10. Secondary osteoporosis (YES/NO).
11. Alcohol 3 or more units per day (YES/NO).
12. Femoral neck BMD (g/cm^2).

In a landmark randomized controlled trial published in *The Lancet* in 2018, involving more than 12,000 women aged 70–85 years, FRAX demonstrated high cost-effectiveness in identifying individuals at risk who may benefit from treatment [13]. This tool assists clinicians in determining which patients are suitable candidates for pharmacological treatment and which may not require it. Notably, FRAX can be directly calibrated based on fracture incidence rates in the target population (defined by country and ethnicity). It also considers mortality as a competing risk, recognizing that higher mortality reduces the likelihood of individuals surviving long enough to experience a fracture. Several novel measures have been proposed to enhance fracture risk assessment in routine practice [4, 13]:

Trabecular Bone Score (TBS): TBS calculates a fracture risk score directly from DXA scans by evaluating spatial variations and pixel grayscale levels. It can be used independently or to refine FRAX output [14].

Lateral Spine X-Rays: This technique detects previously unrecognized vertebral fractures associated with adverse clinical outcomes and the onset of new fractures, including proximal femur fractures [15].

Hip Geometry Measurements: Assessing hip geometry, particularly the length of the hip axis, helps to evaluate fracture risk [16, 17].

Utilizing Prior CT or X-ray Scans: When available, prior scans can be used to estimate BMD, diagnose osteopenia and osteoporosis, or identify previously unrecognized vertebral fractures (opportunistic screening) [18].

Other measures of frailty, such as reduced muscle mass and sarcopenia, are not currently considered by any of the available tools but are known to contribute to fracture risk.

These advancements contribute to more accurate fracture risk assessment and better-informed clinical decisions.

5 Proximal Femur Fractures

5.1 Introduction and Epidemiology

Proximal femur fracture affects approximately 18% of women and 6% of men over the course of their lives. Notably, there are significant variations in annual incidence rates across different countries. For instance, in Norway, the incidence is approximately 439 per 100,000, while in Ecuador, it is 55 per 100,000.

Despite the higher prevalence among women, proximal femur fractures have a more severe prognosis for men. Approximately one-third of male patients face the risk of mortality within a year after sustaining such a fracture.

Within the European Union, there are approximately 500,000 femur fractures reported annually. Of these cases, 400,000 involve women and 100,000 involve men. In Italy, this condition affects 0.8% of the entire population, representing 18% of all traumatic injuries. Notably, 67% of these cases occur in patients over the age of 65.

The ageing population contributes to the rising incidence of femur fractures. This increase can be attributed to both a higher prevalence of osteoporosis and the more frequent occurrence of age-related comorbidities. Overall, in 1990, 1.26 million femur fractures were recorded globally, and it is estimated that by 2050, this number will reach 4.5 million [19, 20].

One of the crucial aspects of proximal femur fractures is their impact on the quality of life and independence of elderly individuals. It is estimated that over 20% of patients require long-term care facilities within a year after the fracture.

Furthermore, proximal femur fractures result in a significant loss of active days due to disability. Surprisingly, this impact is even greater than that of tumorous pathologies, highlighting the social relevance of proximal femur fractures and the need for targeted interventions to prevent and effectively manage them.

In addition to health-related effects and quality of life, proximal femur fractures impose a significant economic burden on healthcare systems and society as a whole. For instance, in the United States, it has been estimated that the direct cost associated with proximal femur fractures in 2010 ranged from 17 to 20 billion dollars [21, 22].

This cost encompasses not only immediate fracture treatment expenses but also costs related to postoperative complications, rehabilitation, and long-term care necessary for recovery and management of the fracture's long-term consequences.

Moreover, indirect costs due to lost productivity and reduced workforce participation by both patients and, to a lesser extent, their caregivers can significantly impact the national economy.

In summary, proximal femur fractures are not merely a medical issue; they also have social and economic implications. Addressing this challenge requires an approach that includes fracture prevention, effective treatment, and appropriate management of long-term consequences to improve the health and well-being of older individuals and reduce their impact on society as a whole.

Proximal femoral fractures tend to occur primarily in the elderly, with the majority of cases happening in their eighth decade of life. In these patients, fractures typically result from low-energy trauma, such as falls from an upright position. In contrast, these fractures are uncommon in the younger population. They usually occur in male patients following high-energy traumas like car accidents or falls from significant heights.

5.2 Classification

Proximal femoral fractures can be classified into two different types based on their location and fracture pattern:

1. Medial Fractures:

   - Involve the intra-articular area, within the joint capsule.
   - Limited Fragmentation: medial fractures are characterized by less fragmentation of the bone fragments. This is due to the presence of the robust joint capsule surrounding the hip joint, which helps to keep the fragments more stable and reduces the risk of complications related to fragmentation.
   - Local Pain: One of the main symptoms of medial fractures is localized pain in the inguinal region. This pain can be sharp and intense, significantly limiting the mobility of the affected individual.
   - Functional Impairment: Medial fractures can cause partial or complete functional impairment of the affected limb. In the case of noncomplete fractures or fractures locked in valgus, the patient may retain joint mobility and load the affected limb, although there is a risk of secondary fragmentation.

Fig. 1 Subcapital femur fracture

Fig. 2 Transcervical femur fracture

- Fracture Position: Medial fractures can be subcapital (Fig. 1) or transcervical (Fig. 2). Additionally, it is crucial to evaluate the fragmentation and direction of the fracture line. Noncomplete fractures with a horizontal line or valgus fragmentation tend to be more stable, whereas fractures with varus displacement or a more vertical line are prone to further fragmentation, leading to greater instability and functional limitation.

2. Lateral Fractures:

- Extra-articular: They involve the portion of the femur between the base of the femoral neck, the greater trochanter, and the lesser trochanter.
- Greater Fragment Disruption: Lateral fractures are characterized by significant disruption of the bone fragments. This is due to the presence of the pelvitrochanteric muscles, which cause fragmentation with clear external rotation and upward movement of the distal fragment, resulting in shortening of the affected limb.
- Local Pain: One of the main symptoms of lateral fractures is intense localized pain. It is felt both anteriorly in the inguinal region and at the trochanteric level, laterally on the thigh. This pain significantly limits the mobility of the affected individual, with the limb typically positioned in external rotation and abduction.
- Functional Impairment: Lateral fractures can lead to complete functional impairment of the affected limb.
- Fracture Position: Lateral fractures can be furtherly classified into basicervical (Fig. 3), pertrochanteric (Fig. 4), or subtrochanteric (Fig. 5). Evaluating the direction of the fracture line is crucial for assessing fracture stability. Fractures involving an intact medial wall, calcar, and lesser trochanter are more stable and less prone to fragmentation. In contrast, fractures that include these structures or exhibit a reverse fracture line (from medial to lateral in a proximal-distal direction) tend to have greater fragmentation of the bone ends. Special attention should be paid to basicervical fractures during reductions, especially when using intramedullary nails, as there is a higher risk of femoral neck rotation, potentially compromising optimal reduction.

Fig. 3 Basicervical femur fracture

Fig. 4 Pertrochanteric femur fracture

Fig. 5 Subtrochanteric femur fracture

5.3 Diagnosis

The diagnosis of a femoral fracture is typically carried out using a standard radiographic examination. This examination should include an anteroposterior projection of the pelvis (Fig. 6) and both anteroposterior and cross-table lateral projections of the affected hip (Fig. 7). In some cases, especially for incomplete or impacted valgus fractures, these fractures may go unnoticed, leading to the risk of undertreatment and further complications. If there is significant doubt about a femoral fracture, it is advisable to resort to second-degree diagnostic techniques. These include Magnetic Resonance Imaging (MRI) as a first choice, as it allows to better assess the fracture line surrounded by bone edema when the fracture is recent (Fig. 8). Unfortunately, MRI is not always available in emergency setting. In these cases, Computer Tomography (CT) scans can be used as a second-degree diagnostic tool [23].

5.4 Treatment

The treatment of femoral fractures is primarily surgical, as the goal is to minimize the patient's immobilization period. Surgical intervention aims to promote early rehabilitation and a rapid return to walking and to performing activities of daily life.

In the case of patients over the age of 65, it is advisable to perform the surgery as soon as possible (within 48 hours, according to Italian guidelines). However, it is also important to consider any pre-existing medical conditions that could influence the decision to undergo surgery or delay it [24–28]. The standard treatment differs for medial and lateral fractures:

Fig. 6 X-ray in anteroposterior projection of the pelvis showing a mediocervical fracture of the femur

Fig. 7 Cross-table lateral projection of a mediocervical fracture of the femur

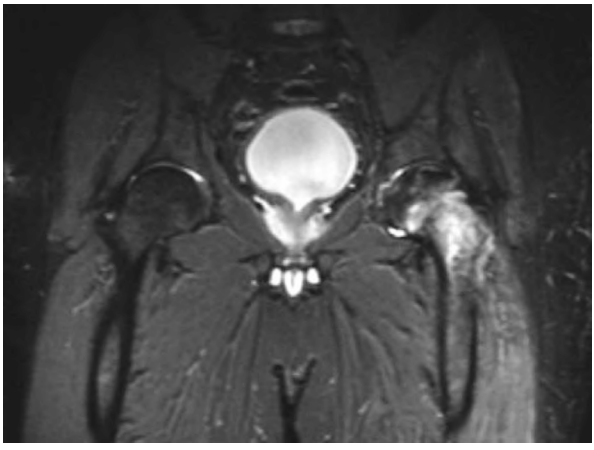

Fig. 8 Magnetic resonance imaging of the pelvis showing a mediocervical fracture of the femur

1. Medial Fractures:
    - These fractures are characterized by the risk of avascular necrosis of the femoral head due to its terminal blood supply.
    - They also have a higher risk of nonunion or delayed healing, because of the anticoagulant properties of intra-articular synovial fluid, which doesn't always allow proper bone callus formation.
    - In young patients or those with incomplete, impacted, or varus fractures, consider attempting osteosynthesis using cannulated screws or specific plates (Fig. 9).
    - For elderly patients or complex fractures, hip arthroplasty (total hip replacement) is advisable (Fig. 10). Total hip replacement can be done in patients under 70 years of age with severe hip osteoarthritis or older patients with nonsignificant comorbidities. In cases of severe comorbidities or patients

Fig. 9 Osteosynthesis using cannulated screws of a mediocervical fracture of the femur

Fig. 10 Total hip replacement of the right hip

over 70 years old, a partial hip replacement (endoprosthesis) is recommended, where only the femoral component is replaced, preserving the native acetabular cavity (Fig. 11).

2. Lateral Fractures:

- These fractures are typically treated with osteosynthesis using either an intramedullary nail (Fig. 12) or a plate, depending on the integrity of the lateral wall.
- Advantages of using an intramedullary nail include avoiding direct fracture site exposure, smaller incisions, shorter surgical times, reduced infection risk, and less muscle trauma.

In cases of significant fragmentation, exploration of the fracture site may be necessary for reduction and cerclage wires can be used to stabilize the fracture (Open Reduction and Internal Fixation, ORIF).

Fig. 11 Partial hip replacement (endoprosthesis) of the left hip

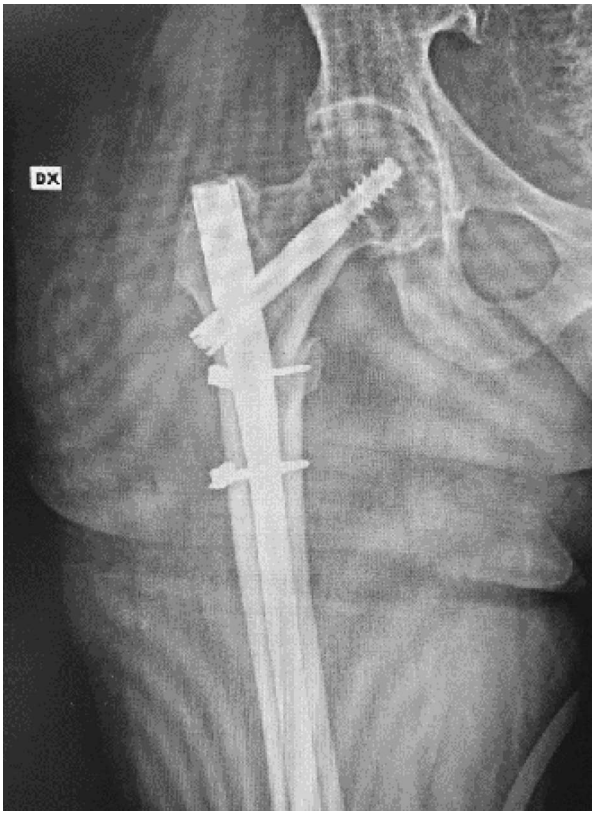

Fig. 12 Intramedullary nail fixation of a perthrocanteric fracture of the femur

5.5 Complications and Adverse Events

Proximal femur fractures have, even with an optimal care, a high rate of complications associated with the age of affected patients, comorbidities, and immobilization [29]. The most common general complications are typically early and result from limited mobility in elderly patients with femur fractures:

- Bronchopneumonia: This complication arises due to immobility, poor ventilation caused by positioning, and pain resulting from the fracture.
- Pressure ulcers (bedsores): These primarily occur in the sacral and calcaneal regions due to supine positioning. They can lead to infections, extensive skin necrosis, and even patient mortality. To prevent them, patients with femur fractures are often placed on antidecubitus mattresses.
- Deep venous thrombosis (DVTs): It is a condition where blood clots form in the deep veins of the body, typically in the legs. The incidence of preoperative DVT following femoral neck fractures ranges from 6.8% to 28% according to different studies [30, 31]. Most patients with DVT have thrombi solely in the injured extremity, but some cases involve the uninjured extremity as well.

Local complications, on the other hand, tend to be delayed and are related to vascularization, implantation, or local infections:

- Delayed union, nonunion, and pseudarthrosis: A condition where bone healing does not occur properly. This can be due to several factors, patient-related or patient-unrelated factors, such as the quality of the osteosynthesis or a peri-implant infection.
- Avascular necrosis of the femoral head: Common in severely displaced femoral neck fractures treated with synthesis. It can occur up to 18–24 months after the intervention.
- Malunion: abnormal healing of the fracture. This can lead to heterometry of the lower limbs.
- Dislocation or mobilization of prosthetic components.
- Peri-implant or periprosthetic infection: One of the most feared complications, it can lead to failure of the implant or synthesis. Treatment may involve antibiotics or surgical intervention, including material removal and definitive resolution of the infection.

5.6 Mortality

The mortality rate associated with femoral fractures is very high, primarily due to the type of patients affected and the general complications that may arise. A higher incidence has been observed in male patients aged over 85 years, particularly those with a Charlson Comorbidity Index greater than 1. The overall mortality rate for femoral fractures increases progressively over time after the fracture occurs. It stands at approximately 4.7% one month after the fracture, rising to 20.7% at one year, and 30.4% at two years [32, 33].

Early surgical fixation, antithromboembolic and anti-infective prophylaxis, good pain control, detection and management of delirium, correct urinary tract management, avoidance of malnutrition, vitamin D supplementation, osteoporosis treatment and promotion of early mobilization, and falls prevention are basic recommendations for an optimal care of hip fractured patients [26–29].

6 Vertebral Fractures

6.1 Introduction and Epidemiology

The spine is the second most common location of osteoporosis-related fractures, following the proximal femur. Typically, vertebral fragility fractures are not associated with trauma. Instead, they are more commonly linked to a collapse of weakened vertebral bodies under axial load (“vertebral sagging”). They occur most

frequently in the thoracolumbar spine. The most affected vertebrae are T12 and L1, followed by L2 and L3.

The epidemiology of these fractures is influenced by the fact that these fractures can be challenging to diagnose, as they often present with few symptoms and may go unnoticed or unrecognized. Moreover, the radiographic criteria for diagnosis may differ among countries, and this can have an influence on the estimated incidence and prevalence. However, comparing men and women in different age groups, the incidence is higher in men under the age of 50–55 years, but after 60 years of age women have a higher risk.

The risk further increases after 70 years. In men, the incidence begins to rise after the age of 70 and more markedly after 80 years of age [34, 35].

The degeneration of the paraspinal musculature plays a fundamental role in the pathogenesis of vertebral fractures. Under optimal conditions, this musculature provides support and protection for the spinal column. Elderly people often experience a generalized gradual loss of muscle mass. This condition is known as sarcopenia. This reduction in muscle strength can directly impact mobility and balance, leading to an increased risk of falls and fractures. In the spinal region, in addition, the support to the spine is lost. This represents a predisposing factor for vertebral collapse.

When a vertebral collapse occurs, the biomechanics of the spine as a whole is altered and the weight on the other vertebral bodies further increases. In fact, each vertebral fracture significantly increases the relative risk of subsequent fractures and vertebral fractures are often diagnosed as multiple.

Interestingly, an association between vertebral fractures and type 2 diabetes mellitus has been observed. These fractures are more common in diabetic patients, even in those with higher T-scores compared to the general population [36].

As previously stated, these fractures often present as paucisymptomatic. The most common presentation is spontaneous pain during loading, in intermittent fashion. Since the pain is mild, it is often ignored even for long periods of time. In rare cases, vertebral fractures can cause myeloradicular compression. Due to their location, the most affected nerves are the sciatic nerve and the crural nerve and the patient develops symptoms like lumbocruralgia, lumbosciatalgia, or peripheral nerve deficits in the most severe cases. The flattening of the vertebral bodies is usually gradual and may worsen over time, until they reach a complete collapse, known as “vertebra plana.” Eventually, the collapse of multiple adjacent vertebrae results in a reduction in the patient’s height and sagittal imbalance (degenerative kyphosis), and the patient starts to notice the inability to perform usual daily activities, such as reaching a shelf. Usually, at this point, the patient is prompted to seek medical attention. On digital pressure, pain localizes around the spinous processes and the involved paravertebral masses.

From a socioeconomic perspective, these fractures are a source of disability and loss of autonomy, especially when they occur repeatedly. For this reason, it is crucial to have an early diagnosis and an adequate treatment.

6.2 Classification

There are various classification systems for these fractures.

- The *Genant classification of vertebral fractures* [37] (Fig. 13) is based on the shape of the vertebrae, considering the loss of height involving the anterior, posterior, and/or middle vertebral body. This classification helps define and monitor the morphology of fractures over time. It considers both the percentage of deformity and the fracture morphology.

    0. Grade 0: Normal vertebra
    1. Grade 1: Mild fracture with less than 25% loss of height.
    2. Grade 2: Moderate fracture with 26–40% loss of height.
    3. Grade 3: Severe fracture with more than 40% loss of height.

- The *AO Spine Thoracolumbar Injury Classification System* [38, 39] divides these fractures into three types (A, B, and C), which are further subdivided into various subtypes. Osteoporotic fractures, in most cases, fall into type A1, known as "Wedge-compression" fractures. These fractures are characterized by an intrinsic stability, as they do not involve the posterior tension band. However, any possible instability should be ruled out with Magnetic Resonance Imaging (MRI) before the treatment is chosen. When an A1 fracture is confirmed, this classification suggests in general nonoperative treatment with bracing. Depending on the severity of the wedging and the local kyphosis, surgery may be indicated. The *AO Spine—DGOU Osteoporotic Fracture (OF) Classification System* [40] is a treatment score based on a classification designed for osteoporotic fractures of the thoracolumbar spine in patients with osteoporosis. Here are the details of the classification:

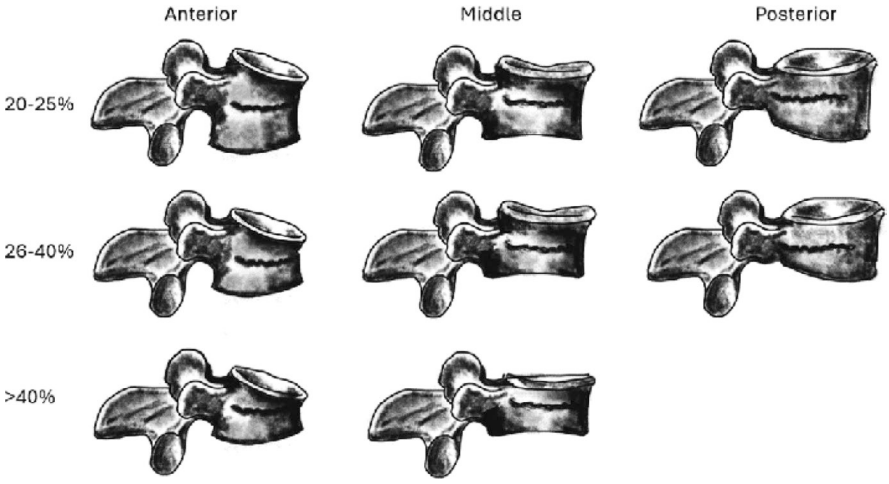

Fig. 13 The Genant classification of vertebral fractures

1. OF1: These fractures are not characterized by vertebral deformities but only by edema. They are typically not visible on X-rays but may be detected on MRI (STIR sequence).
2. OF2: Deformation of one endplate without or with only minor posterior wall involvement (with posterior wall <1/5 involvement).
3. OF3: Deformation of one endplate with distinct posterior wall involvement (with posterior wall >1/5 involved).
4. OF4: Deformation of both endplates with or without posterior wall involvement, resulting in loss of vertebral frame structure, vertebral body collapse, or "pincer type" fractures.
5. OF5: Trauma with anterior or posterior tension band failure, including injuries with signs of distraction, rotation, or translation.

The scoring system integrates this classification with other parameters. A score greater than six indicates surgical treatment, while a lower score suggests conservative management.

6.3 Diagnosis

The diagnosis for this type of fractures is usually performed using instrumental exams and can also be accidental during tests conducted for other pathologies.

The recommended exams include the following:

- X-ray of the spine in two standard projections (Figs. 14 and 15): This is useful for observing vertebral collapse, evaluating the size of vertebral bodies, and detecting any spinal deformities. It serves as a primary-level examination.
- CT (Figs. 16 and 17): CT scans allow for more accurate assessment of the fracture pattern, classification, and identification of fractures not clearly visible on X-rays.
- MRI: MRI helps date a fracture by evaluating the presence of bone edema (especially in STIR sequences) and any myeloradicular compressions.
- Blood tests: Similar to general osteoporosis assessments, first- and second-degree blood tests can complement the evaluation of vertebral fractures. In cases of multiple vertebral collapses, especially if nontraumatic, alternative diagnoses should be considered. Additionally, the presence of associated conditions such as multiple myeloma and monoclonal gammopathy of uncertain significance (MGUS) should be evaluated, as they may be related to the occurrence of these types of fractures.

Fig. 14 Anteroposterior X-ray of the lumbar spine

6.4 Treatment

The treatment should aim to prevent any subsequent fractures by identifying the etiology and avoiding the progression of the fracture into a vertebral collapse. An accurate evaluation of the patient, their comorbidities, and functional needs is essential.

Conservative Treatment

Conservative treatment is the primary approach whenever possible. The milestone of conservative treatment is spinal bracing. The purpose of a brace is to prevent ranges of motion outside of limits deemed unfavorable for fracture healing. This provides stability during the healing process and reduces the pain due to excessive movement. This treatment can be scarcely tolerated by some individuals because of the inconveniency for daily activities, the onset of skin irritation or pressure sores,

Fig. 15 Lateral X-ray of the lumbar spine

and the psychological impact of the procedure [41, 42]. Different types of orthoses are available based on the fracture location:

- Thoracolumbar sacral orthosis (TLSO): It is used for fractures between T8 and L4.
- TLSO hyperextension brace or three-point brace: Useful for treating fractures in the lumbar or low thoracolumbar region (T10-L2).
- TLSO with cervical extension: Fractures of high thoracic spine (T1-T7).
- TLSO with leg extension: Fractures of the lower spine (L5-sacrum).
- Shoulder straps brace: Suitable for thoracolumbar fractures.

Spinal braces should be kept in place for three months to allow for optimal fracture healing. Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful for pain management and can be taken orally or applied via medicated patches to manage vertebral fractures, minimizing the side effects associated with oral administration.

Pulsed Electromagnetic Field (PEF) is a promising novel technique that involves using magnetic fields to promote healing and reduce pain. It is not routinely used yet in the treatment of vertebral fractures, since its efficacy needs definitive studies to be confirmed [43, 44].

Fig. 16 CT scan of the lumbar spine (sagittal plane)

Surgical Treatment

Surgical treatment is reserved for cases where conservative therapy fails or in the presence of severe deformities:

- Vertebroplasty and kyphoplasty are percutaneous, minimally invasive vertebral augmentation procedures (VAPs). During these procedures, cement, most commonly polymethylmethacrylate (PMMA), is injected into the fracture under image guidance. It is essential to rule out any instability of the fracture and/or any myeloradicular compression before performing these procedures. Vertebroplasty involves the direct injection of cement into the trabecular vertebral body, whereas kyphoplasty is performed by inserting an inflatable balloon before cement is inserted. The main indications are refractory pain nonresponsive to conservative treatments, persistent edema, or contraindication or intolerance to a brace.
- Vertebral stabilization is used for posttraumatic deformities, unstable fractures, or those involving the spinal canal. Different types of screws can be used, along with hooks and sublaminar bands.

Fig. 17 CT scan of the lumbar spine (coronal plane)

7 Distal Radius Fractures

7.1 Introduction and Epidemiology

The distal radius is the larger of the two forearm bones and is positioned radially. The distal end of the radius is defined as the area approximately three centimeters proximal to the radiocarpal joint, where the radius interfaces with the scaphoid and lunate bones of the wrist. Distal radius fractures are typically caused by a fall onto an outstretched hand. They are one of the most common bone injuries in osteoporotic patients, representing about one-sixth of all adult fractures presenting to the emergency department.It significantly impacts wrist functionality and patients' quality of life. Distal radius fracture can significantly compromise the patient's ability to use the wrist and hand normally [45, 46].

In general, there are two distinct peaks in frequency: one among young males aged 10 to 16 years and another among elderly women aged 58 to 86 years. In young males during adolescence, distal radius fractures are often the result of falls during sports activities, such as soccer, basketball, or skateboarding. The second peak frequency of distal radius fractures occurs in elderly women. This phenomenon is closely related to osteoporosis and an increased risk of falls. The loss of bone

density makes bones more vulnerable to minor impacts, thereby increasing the risk of fractures even following relatively mild falls [47, 48].

One of the most noticeable features is the presence of swelling or edema in the wrist area. This swelling can be visually evident and may be accompanied by an increased sensation of tension in the region. The patient may report localized pain in the wrist area, which can be sharp or dull depending on the severity of the fracture. The pain can be intensified by wrist movement or palpation of the affected area. The patient may experience difficulty in performing specific wrist movements, such as flexion, extension, or rotation. In some cases, the fracture can cause a visible deformity or an abnormal deviation of the wrist axis. Dorsal fork deformities are very common in Poteau-Colles fractures, which typically occur from falls on an extended wrist, and volar fork deformities are common in Goyrand-Smith fractures, which are due to falls on a flexed wrist.

7.2 Diagnosis

After the clinical evaluation of the patient, different diagnostic tools can be used to diagnose a distal radius fracture, assess its severity, and determine which treatment is the best option for each patient. Since we are dealing with elderly patients, it is crucial to thoroughly evaluate the patient as a whole with an in-depth medical history. This can be useful to narrowing down possible alternative diagnoses, assess individual risk factors and tailor treatment plans.

- X-ray: X-rays are always the primary diagnostic imaging modality for evaluating distal radius fractures. Wrist X-rays in two projections (anteroposterior and lateral) provide a detailed view of the wrist bones (Fig. 18). X-rays help determine the fracture's position, extent, and angulation.

  In 1979, Cooney first formulated instability criteria to assess early fractures, which are more likely to fail conservative treatment [49]. A fracture is considered unstable if one or more of the following criteria is met:

  – Dorsal angulation >20°.
  – Radial shortening >5 mm.
  – Dorsal comminution.
  – Intra-articular involvement.

  In 1989, Lafontaine proposed his version of instability criteria to predict the risk of secondary displacement [50]. A fracture is considered unstable if three or more of the following criteria is met:

  – Dorsal angulation >20°.
  – Dorsal comminution.
  – Intra-articular radiocarpal fracture.
  – Associated ulnar fracture.
  – Age > 60 years.

Fig. 18 Wrist X-rays in two projections (anteroposterior and lateral) showing a distal radius fracture

Many other instability criteria have been proposed since then; at the present time consensus is lacking about the best predictive factors for fracture instability [51, 52].

- Computed Tomography (CT): CT can be used to assess more complex fractures, especially articular fractures or cases where standard X-rays do not provide a clear image of the lesion. CT offers a three-dimensional visualization of the bones and allows for a more detailed evaluation of the fracture, including precise assessment of any joint steps or depressions.
- Ultrasound or MRI: In cases of uncertain tendon or ligament injuries.

7.3 Treatment

After the diagnosis of a distal radius fracture, the patient undergoes an initial evaluation to determine the severity of the injury and the appropriate treatment. In the case of a displaced fracture, a reduction maneuver is often necessary to properly realign the bones. This procedure is performed under local intrafocal anesthesia, where an anesthetic is injected directly into the fracture area to alleviate pain. After

the fracture reduction, a plaster cast is applied around the wrist area to stabilize the fracture, maintaining it in the reduced position. The cast must be correctly applied to ensure adequate support and alignment of the fractured bones. Following the reduction and application of the cast, a repeat X-ray is performed to assess the correct position of the cast and the proper reduction of the fracture.

At this point, based on the obtained result, an assessment must be made to decide whether the treatment will be conservative or surgical. Conservative treatment is the current gold standard for most distal radius fractures. However, surgical treatment should be considered in patients with few comorbidities due to the advantages it offers in terms of excellent functional outcomes. These advantages include the ability to mobilize fingers and the elbow early, remove the cast approximately 15 days after the procedure, and facilitate early rehabilitation compared to conservative treatment. However, in most studies, at one-year follow-up, clinical scores show no significant differences in wrist pain and function between conservative and surgical treatment [53, 54].

Conservative Treatment

Conservative treatment of distal radius fractures is a common approach for managing correctly reduced injuries, nonarticular fractures, or articular fractures with step-offs less than 1–2 mm, aiming to promote healing without the need for invasive surgical interventions, considering the average age of patients with fragility fractures (Fig. 19).

After applying the cast, it is essential to inform the patient of the need for a follow-up X-ray examination after one week to reassess any displacements and evaluate the presence of peripheral pulses. Proper cast placement is crucial to prevent the development of intolerance. If no complications arise, conservative treatment with a plaster cast is continued for one month. At this point, a new X-ray check is performed and the cast is removed, initiating wrist mobilization aimed at functional recovery.

Surgical Treatment

Surgical indication is considered if

- The reduction is unsatisfactory or if the fracture is highly complex, especially in intra-articular fractures.
- The fracture falls within instability factors before reduction.

Fig. 19 Wrist X-rays in two projections (anteroposterior and lateral) showing a distal radius fracture that has been reduced and immobilized in a cast

- The postreduction X-ray in the cast shows dorsal angulation >0°, volar angulation >10°, ulnar shortening >5 mm, ulnar plus, articular displacement >1–2 mm, and incongruence of the distal radioulnar joint (RUD).
- There is cast displacement at the 7-day follow-up or intolerance to the cast and any splints. Surgical treatment is generally performed with plates and screws for closed fractures or external fixation in cases of open fractures or soft tissue compromise (Fig. 20). These implants are considered today the gold standard for the open reduction and internal fixation of this type of fractures [55–57].

Fig. 20 Wrist X-rays in two projections (anteroposterior and lateral) showing a distal radius fracture that has been reduced and fixed with plate and screws

8 Proximal Humerus Fractures

8.1 Introduction and Epidemiology

Proximal humerus fractures are very common, representing 5–6% of all fractures and 10% of fractures in patients over 65 years old. The "lifetime risk" in a woman over 50 years old is 13%. In this case as well, there are two peaks in frequency: in young individuals due to high-energy trauma, and in the elderly population due to low-energy falls [58].

Humerus fractures are often difficult to interpret, because in most cases, they are multifragmentary. Typically, the parts that tend to fracture are the head, tuberosities, and the diaphysis at the surgical neck level. Due to significant deforming forces, it is very common for this type of fracture to result in fragmentation. In fact, muscles tend to break down the various fragments:

- The pectoralis major muscle breaks down the diaphysis anteromedially.
- The supraspinatus, infraspinatus, and teres minor muscles break down laterally and externally rotate the trochlea.
- The subscapularis muscle breaks down the head and trochlea internally.

Usually, these fractures are caused either by falling over the outstretched hand, with an indirect mechanism, or by a direct fall on the shoulder.

The patient typically presents to the emergency department with the arm positioned alongside the body, supported by the contralateral side. Swelling and dull pain can be observed immediately, and anatomical deformity of the shoulder profile may be visible in cases where there is a dislocation of the humeral head associated with the fracture. Humerus fractures cause a typical hematoma that develops a couple of days later and spreads to the medial aspect of the arm and the lateral aspect of the ipsilateral hemithorax: Hennequin's hematoma.

8.2 Classification

There are several classifications for proximal humerus fractures. The most significant are described as follows:

- *Neer Classification* [59] (Fig. 21): Created by Neer in 1970. It is based on the study of 300 proximal humerus fractures treated over 14 years. Neer divides the humerus into four main fragments according to Codman's subdivision: the greater tuberosity, lesser tuberosity, articular surface, and diaphysis. Fractures are considered displaced if they have at least 1 cm of distance and/or an angulation greater than 45° between two or more fragments, based on the number of fragments present. The higher the number of fragments, the greater the likelihood of avascular necrosis of the humeral head.
- *Hertel Classification* [60]: Also known as the "LEGO classification," it also uses Codman's subdivision. Each "brick" represents a bony fragment. It combines the five basic fracture planes and provides a total of 12 fracture patterns: six with 2 fragments, five with 3 fragments, and one with four fragments. It was developed

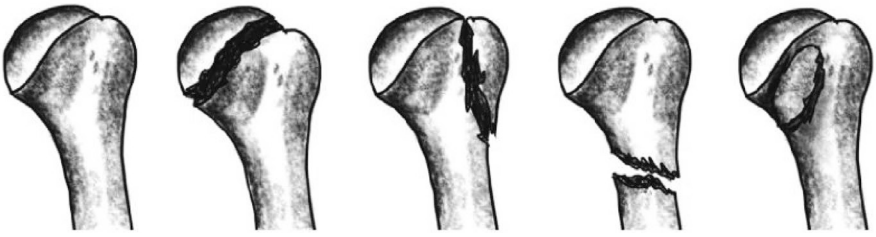

Fig. 21 The Codman's subdivision of proximal humerus fractures: fracture of the greater tuberosity, the lesser tuberosity, the articular surface, and the diaphysis

to assess head perfusion and the risk of osteonecrosis. The closer the pattern is to 12, the higher the likelihood of osteonecrosis.

Superiority of either classification system has not been proved; both these systems have high intraobserver and interobserver reproducibility [61].

8.3 Diagnosis

The diagnosis of proximal humerus fractures must be very accurate due to their tendency to be multifragmentary and often displaced. It should guide the physician toward the appropriate treatment:

- Radiography: X-rays are the primary diagnostic imaging method for evaluating proximal humerus fractures. Shoulder radiographs should include the following:
  - True anteroposterior view: This provides adequate visualization of the joint.
  - Lateral view: Usually performed transthoracically due to the patient's functional limitations.
  - Additionally, a Y-view may be useful to assess for any dislocations.

  These images help determine the position, number of fragments, extension, and angulation of the fracture.
- Computed Tomography: CT is essential for multifragmentary proximal humerus fractures. It allows precise visualization of fragment positions and origins, including nonvisible fracture lines on X-rays. CT provides a three-dimensional representation of the bones and is useful for preoperative planning.
- Other Diagnostic Methods: Typically, additional techniques like ultrasound or MRI are not necessary for proximal humerus fractures. However, they may be useful for studying conditions such as rotator cuff injuries.

8.4 Treatment

The treatment of proximal humerus fractures has always been a subject of debate. Typically, most of these fractures are managed nonsurgically, favoring conservative treatment, especially in elderly patients with complex or two-part fractures. This preference is due to the comparable outcomes of surgical versus conservative treatment and the complications associated with invasive procedures [62]. There are both absolute and relative indications for surgical treatment:

- *Absolute indications*:
  - Open fractures.
  - Neurovascular injury.
  - Fracture dislocations.

- *Relative indications*:
  - Displaced (>5 mm) tuberosity fractures.
  - 40% articular surface comminution
  - Off-ended two-part surgical neck fractures.
  - Two-, three-, four-part fractures where articular surface is displaced >30°.
  - Head-splitting.
  - Young patients with high functional demand.

Various surgical treatment options exist. For fractures with a lower risk of avascular necrosis or in young patients, plate and screw fixation is preferred. In cases of surgical neck fractures, intramedullary nails may be used. For more complex fractures, prosthetic replacement is considered. Anatomic or reverse prostheses are currently the most commonly used. In patients with multiple comorbidities or exposed fractures, external fixation or percutaneous fixation may be necessary. It is essential to inform the patient that both surgical and conservative treatments may not result in excellent outcomes and a complete return to normal function [63, 64].

Questions for Self-Assessment

1. Which of the following is the most common imaging technique for diagnosing proximal humerus fractures?

   (a) MRI.
   (b) CT scan.
   (c) X-ray.
   (d) Ultrasound.

   Correct answer: (c) X-ray.
2. Which of the following is an absolute indication for surgical treatment of proximal humerus fractures?

   (a) Displaced tuberosity fractures.
   (b) Neurovascular injury.
   (c) Articular surface comminution.
   (d) Two-part surgical neck fractures.

   Correct answer: (b) Neurovascular injury.
3. What is the main advantage of using a CT scan for proximal humerus fractures?

   (a) It provides better visualization of the soft tissue injuries.
   (b) It offers a detailed three-dimensional view of bone fragments.
   (c) It is less expensive than X-rays.
   (d) It helps in detecting fractures in the elbow joint.

   Correct answer: (b) It offers a detailed three-dimensional view of bone fragments.

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Pharmacological Therapies

Osteoporosis Drugs: Old and New Drugs

Boselli Federica and Maria Grazia Radaelli

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Chapter Introduction: What You Will Learn in This Chapter
This chapter examines the role of osteoporosis pharmacological therapies in the management of skeletal fragility in patients with diabetes mellitus. While traditional bone mineral density (BMD) metrics may not fully capture fracture risk in diabetic individuals, targeted osteoporosis treatments may still confer benefit. However, efficacy, safety, and underlying pathophysiology must be carefully considered.

This chapter will provide an overview of the available antiosteoporotic drugs, review the evidence for their use in diabetic populations, and highlight key clinical considerations for personalized treatment.

Key Points
- The unique challenges of managing osteoporosis in diabetes
- Mechanisms of action and effects of key osteoporosis drugs (bisphosphonates, denosumab, teriparatide, romosozumab)
- Evidence for drug efficacy and safety in T1DM and T2DM

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- Drug-specific considerations: renal function, cardiovascular risk, bone quality
- Clinical recommendations for treatment personalization

Learning Objectives
By the end of this chapter, you will be able to:

- Identify the main classes of osteoporosis drugs and their mechanisms of action.
- Discuss the specific evidence base for the use of osteoporosis therapies in diabetic patients.
- Evaluate the risks and benefits of pharmacological choices based on diabetes type and complications.
- Apply an individualized approach to osteoporosis treatment in diabetes mellitus.

Definitions
- Antiresorptive therapy: A class of drugs that slow bone resorption, primarily including bisphosphonates and denosumab.
- Anabolic therapy: Osteoporosis treatments that stimulate bone formation, such as teriparatide and romosozumab.
- Denosumab: A monoclonal antibody that inhibits RANKL, reducing bone resorption and increasing BMD; shown to improve bone quality in diabetes.
- Teriparatide: A recombinant form of PTH that stimulates osteoblastic activity; may be particularly useful in diabetes with low bone turnover.
- Romosozumab: A sclerostin inhibitor with dual action (anabolic and antiresorptive); efficacy in diabetic osteoporosis is under investigation.

1 Introduction

Osteoporosis is a systemic skeletal disease characterized by a decrease in bone mass and microarchitectural deterioration of bone tissue, resulting in bone fragility and increased fracture risk. It is a condition that affects approximately 200 million people worldwide, particularly postmenopausal women, in which fragility fractures are very common and are associated with increased morbidity, mortality, and healthcare costs [1, 2].

Proper management of osteoporosis is highly cost saving considering the relatively low costs for the pharmacological interventions for this condition.

Current medications approved for postmenopausal osteoporosis can be divided into two major categories: antiresorptive drugs and osteoanabolic drugs. Antiresorptive drugs inhibit osteoclast-mediated bone resorption, thus increasing bone mineral density, and prevent the progression of structural damage but may not restore skeletal architecture. However, osteoanabolic drugs stimulate bone formation, improve bone strength, and restore microarchitectural deterioration of bone tissue.

Moreover, a dual-acting agent that at the same time stimulates bone formation and inhibits bone resorption, romosozumab, has been recently approved by regulatory agencies as a treatment option for postmenopausal osteoporosis [3].

Other than pharmacological interventions, lifestyle measures are recommended for fracture prevention. These include avoiding cigarette smoking and excessive alcohol intake as well as practicing regular physical activity [4, 5].

2 Intake of Calcium and Vitamin D

Because the efficacy of most osteoporosis treatments has been studied in association with calcium and vitamin D supplementation, and some osteoporosis medications can cause hypocalcemia, adequate calcium and vitamin D intake is recommended [4].

Most guidelines recommend 1000–1200 mg of calcium daily in women with postmenopausal osteoporosis and suggest prescription of calcium supplements only when an adequate dietary intake cannot be achieved, thus reducing the associated potential risk of nephrolithiasis. A daily amount of 400–2000 IU of vitamin D is also recommended to promote calcium absorption that is necessary for mineralization of bone. Supplemental vitamin D should be administered to achieve and maintain serum 25-hydroxyvitamin D levels to approximately 30 ng/mL (75 nmol/L) [6, 7].

3 Bisphosphonates

Bisphosphonates (BPs) are considered the first-line agents for treatment of osteoporosis.

They bind to hydroxyapatite crystals at the surface of the bone matrix and are incorporated into areas of active bone remodeling. Through the inhibition of the activity of farnesyl pyrophosphate synthase, this group of drugs can prevent the recruitment of osteoclasts and induce the apoptosis of these cells, leading to the suppression of osteoclast-mediated bone resorption and ultimately increasing BMD and bone strength [8, 9].

Among this class of drugs, those licensed for the treatment of postmenopausal osteoporosis are alendronate, risedronate, ibandronate, and zoledronic acid. They show some differences in potency, pharmacokinetics, and persistence of action. The effect of some bisphosphonates on bone resorption markers is earlier than others: for example, zoledronic acid has more rapid effects than alendronate. Alendronate and zoledronic acid exhibited a prolonged effect after treatment discontinuation, while risedronate showed a more rapid offset. This might be explained by the fact that the affinity of alendronate and zoledronic acid for hydroxyapatite is greater than that of risedronate [10, 11]. Moreover, alendronate, risedronate, and zoledronate could reduce the risk of vertebral, nonvertebral, and hip fractures by about 50%–70%, 30%, and 40% respectively, while ibandronate has not been shown to be effective in reducing the risk of hip fractures [5, 12, 13].

There is supporting evidence of the prolonged benefits of BPs on fracture prevention and BMD maintenance for years during treatment [14]. These drugs may be retained for up to 10 years in the bone matrix [15]. The results of a multicenter study by Bone et al. published in 2004 showed that a 10-year use of alendronate in postmenopausal women was associated with a significant increase of BMD at the lumbar spine (13.7%), femoral neck (5.4%), and total hip (6.7%) [16].

Another multicentric study, the Fracture Intervention Trial Long-term Extension (FLEX), evaluated the effects of extended treatment with oral BPs (10 years) compared with the 5-year use in 1099 postmenopausal women, reporting a significant increase in serum levels of bone turnover markers and a statistically significant decrease in BMD at the lumbar spine and total hip in women who discontinued alendronate after 5 years of therapy compared with those that maintained alendronate for 10 years. Moreover, the rate of clinical vertebral fractures in the group treated with alendronate for 10 years was significantly lower when compared to the group that switched to placebo after 5 years of treatment (2.4% vs. 5.3%, respectively, with a relative risk reduction of 55%) [15].

The long-term effects of zoledronate 5 mg were assessed in the The Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) study. Postmenopausal women randomized to receive treatment with annual infusions of zoledronate for 6 years had higher values of BMD at the lumbar spine and at the femoral neck compared with the group that switched to placebo after 3-year zoledronate therapy, as well as a lower risk of morphometric vertebral fractures (3.0% vs. 6.2%, respectively) [17]. The result of these studies suggested an additional benefit from continuous treatment with alendronate for up to 10 years or 5 mg yearly of zoledronate for up to 6 years in postmenopausal women at high risk of fractures.

Therefore, according to the task force of the American Society for Bone and Mineral Research, postmenopausal women receiving oral BP for ≥5 years or intravenous BP for ≥3 years and high risk of fractures (obtained using fracture risk calculators or defined by hip, spine, or multiple other osteoporotic fractures before or during therapy or hip BMD T-score of ≤ −2.5 SD) should be evaluated for maintaining BP treatment or switching to another antifracture therapy and should be reassessed every 2–3 years. The task force also recommended that clinicians consider a drug holiday only in patients who are thought to be at moderate or low risk of fragility fractures [18].

Bisphosphonates are not recommended in case of severe renal impairment as defined as a glomerular filtration rate of <30 mL/min or in patients with evidence of acute renal failure [9].

The adverse events of BP treatment can be divided into short-term and long-term effects. Among short-term adverse events related to treatment with oral BPs, upper gastrointestinal tract irritation is common. Consequently, contraindications to oral BPs include esophageal stricture, achalasia, or Barrett esophagus, whether a remote history of peptic ulcer disease or the presence of gastroesophageal reflux well controlled with medications do not represent an absolute contraindication to these drugs use.

Patients intolerant to oral BPs could not maintain an upright posture for 30–60 min after oral administration and this could result in the establishment of erosive esophagitis [19]. This led to the development of novel oral bisphosphonate formulations such as buffered, effervescent alendronate, and gastro-resistant risedronate [20].

Approximately 10%–30% of individuals that receive the first infusion of zoledronic acid experience an acute phase reaction of 24–72 h duration characterized by flu-like symptoms (headache, arthralgia, myalgia in association with transient fever) within a few days from the intravenous injection. Symptoms are generally relieved by the administration of paracetamol or ibuprofen.

Moreover, another side effect that is associated with intravenous BP infusion is hypocalcemia, occurring more frequently in patients with renal impairment, hypovitaminosis D, or unrecognized cases of hypoparathyroidism [21].

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF) are extremely rare but serious adverse events related to the long-term use of oral and intravenous bisphosphonates that were initially reported from postmarketing surveillance 10 years after BP approval for osteoporosis treatment [22].

Osteonecrosis of the jaw is defined as the presence of exposed bone in the maxillofacial region that does not heal within 8 weeks in patient with history of antiresorptive and/or antiangiogenic therapy, and in the absence of previous radiation therapy to head and neck. Known risk factors for the development of ONJ are the prolonged exposure to antiresorptive treatment, a history of cancer, chronic use of glucocorticoids (or antiangiogenic, antithrombotic, immunosuppressants, proton pump inhibitors), smoking, hypertension, rheumatoid arthritis, or diabetes mellitus, as well as invasive oral procedures, poor oral hygiene, inflammatory oral diseases, and dental infections.

The association of bisphosphonate use with osteonecrosis of the jaw was initially described in patients with metastatic cancer who were treated with high-dose intravenous bisphosphonates for hypercalcemia of malignancy. Although the frequency of this disorder in oncology patients receiving high-dose bisphosphonates has been reported to be 1%–10%, estimates of its incidence in patients receiving smaller doses of bisphosphonates for the management of osteoporosis are substantially lower, ranging from about 0.001% to 0.01% [23, 24].

Atypical femoral fractures are subtrochanteric or femoral shaft fractures that usually occur spontaneously or with minimal trauma, may be preceded by thigh or groin pain, and may occur bilaterally. They are caused by the accumulation of microdamage or microcracks and reduced bone strength related to long-term use of BPs [12].

Other risk factors for the occurrence of AFF include low levels of 25-hydroxyvitamin D, diabetes, use of glucocorticoids, low total hip BMD, history of falls, older age, and femoral shape [25].

In studies that examined the association of BP treatment with rates of these fractures, incidence ranges from 3.2 to 50 cases per 100.000 person-years with short-term use (<5 years) and approximately 113 per 100.000 person-years with long-term use (>5 years) [26].

All evidence considered, in individuals with osteoporosis at moderate or high fracture risk, the benefit provided by bisphosphonates in reducing fracture incidence far outweighs the very small risk of osteonecrosis of the jaw or of atypical subtrochanteric femoral fractures [22].

4 Denosumab

Denosumab represents the first human monoclonal antibody developed for the treatment of osteoporosis.

It was approved for treatment of postmenopausal osteoporosis in 2010 on the basis of the findings of the FREEDOM trial, and it later received approval for treatment of osteoporosis in men, glucocorticoid-induced osteoporosis, and bone loss due to aromatase inhibitor or androgen deprivation therapies for breast or prostate cancer [27].

Denosumab binds to receptor activator of nuclear factor kappa-B ligand (RANKL) to prevent receptor activation of RANK expressed on mature osteoclasts and their precursor cells, thus inhibiting osteoclast formation, function, and survival [28]. Its administration at the dosage of 60 mg as a subcutaneous injection every 6 months leads to the suppression of osteoclast-mediated bone resorption and to the consequent reduction of fracture risk [29].

In the FREEDOM trial, the subcutaneous administration of 60 mg of denosumab twice yearly for 36 months significantly reduced the risk of new vertebral fracture by 68%, nonvertebral fracture by 20% and hip fracture by 40% relative to placebo [30]. Denosumab also increased BMD at various skeletal sites, including the total hip, lumbar spine, femoral neck, and decreased serum bone turnover markers [30], at a greater extent when compared to bisphosphonates [31, 32].

In the FREEDOM Extension study, prolonged treatment with denosumab for up to 10 years was associated with conserved low rates of vertebral fracture, further reduction in nonvertebral fracture risk along with progressive increases in BMD [33].

Different from bisphosphonates, for which a plateau in hip BMD is generally observed after 3–4 years of treatment, therapy with denosumab is associated with a continued gain in bone density [27].

Possible adverse events associated with this treatment include eczema, cellulitis, nausea, and injection site reactions [30].

Denosumab was generally well tolerated over up to 10 years' treatment in clinical trials and rates of osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) were very low [33, 34]. In particular, the incidence of ONJ in patients who receive the osteoporotic treatment dose of denosumab (60 mg twice yearly) is estimated to be 1/10,000 to 1/100,000 patient-years compared with <1/100,000 person-years in the general population [35, 36].

Denosumab can be used in presence of contraindications or intolerance to oral or intravenous bisphosphonates or in case of severe renal impairment (e.g., CrCl <30–35 mL/min/1.73 mq) without dose adjustment [37].

Several studies demonstrated efficacy and safety of this drug between subjects with mild-to-moderate chronic kidney disease (stages 1–3), suggesting it is generally well tolerated in patients with renal impairment, although they should be monitored for hypocalcemia [38, 39]. Indeed, during the Extension study, hypocalcemia was noted very rarely, but in postmarketing surveillance phase, cases of severe hypocalcemia have been reported, especially in patients with severe renal impairment, hypoparathyroidism, or vitamin D deficiency [40]. Therefore, before initiating the drug, measurement of serum calcium and 25-hydroxyvitamin D levels and correction of hypocalcemia and hypovitaminosis D are mandatory [41].

Because of the lack of affinity for bone mineral, a great concern of denosumab treatment is the rapid reversal of its effects on bone remodeling at the end of the 6-month dosing interval. For this reason, strict and consistent adherence to the dosing regimen is essential. It was observed that after discontinuation of 2 years treatment with denosumab, BMD returned to baseline within 1 year but stabilized near the pretreatment level during the second year, meaning that most of the bone loss occurs during the first year off treatment [42]. A rebound increase in bone turnover markers was also reported, with C-terminal telopeptide of type 1 collagen (CTx) increasing above pretreatment levels within 3 and 6 months and being maximally increased 12 months after the last injection [27, 43].

The clinical consequence of such a rebound in bone turnover after stopping denosumab is increased risk of multiple vertebral fractures. In a post hoc analysis of the FREEDOM trial, prior vertebral fracture was the strongest predictor for multiple vertebral fractures after denosumab discontinuation (OR 3.9), followed by off-treatment duration (OR 1.6) [43, 44]. In another study, longer duration of treatment was also identified as being associated with a higher number of VFs [45].

So, after denosumab withdrawal, transitioning to another anti-osteoporosis therapy is required to reduce the transient rebound of bone turnover that is responsible of rapid BMD loss and increased risk of multiple vertebral fractures. A proposed strategy is the administration of oral or intravenous bisphosphonates but there is a scarcity of data on the optimal duration of bisphosphonate therapy after denosumab discontinuation [46–48].

The European Calcified Tissue Society (ECTS) recommends performing a DXA 6 months after the last denosumab injection and switching from denosumab to oral bisphosphonates or zoledronic acid in case of short-term duration of denosumab therapy (up to 2.5 years) and zoledronate in case of long-term denosumab treatment (more than 2.5 years). Additionally, it is advised to measure bone turnover markers 3 and 6 months after starting alendronate or zoledronic acid to ensure that CTX levels remain within the lower half of the premenopausal reference range. In case of persistently increased bone turnover markers after 3 or 6 months, then a second infusion of zoledronate should be considered [49].

Generally, BMD is maintained or increased when short-term denosumab ($\leq$2.5 years) is followed by antiresorptive medication. However, a single infusion of zoledronate might not be sufficient to maintain BMD over time (>12 months) even after discontinuing short-term denosumab. Longer denosumab-treatment duration

(>2.5 years) is associated with greater bone loss, so multiple BP infusions are required to better control bone turnover [43].

For patients who stop denosumab and experience rapid bone loss despite bisphosphonate administration, retreatment with denosumab is suggested since it may restore bone mineral density [27].

Although there is a maximum follow-up time of 10 years for published clinical data on the long-term effects of therapy with denosumab, there is no absolute limit on treatment duration; therefore, in some patients at continued high risk for fracture, treatment could be continued indefinitely. The optimal duration of denosumab treatment should be evaluated on an individual basis considering potential risks and benefits and a periodic reassessment of fracture risk is recommended to decide whether to continue therapy [27, 41].

As regards sequential treatment, the use of anabolic agents first, followed by antiresorptive therapies, is more effective in reducing fracture risk rapidly and producing further BMD increases. In the FRAME study, a 12-month treatment with denosumab in subjects previously receiving bone-forming agent romosozumab for a year was associated with a sustained reduction in fracture risk and large gains in BMD across the 24-month treatment sequence [50].

In the Denosumab and Teriparatide Administration (DATA) study, treatment with a combination of teriparatide and denosumab achieved larger increases in BMD in the initial 12 months of osteoporosis treatment than did either drug alone. The advantage of combination therapy was maintained but did not increase further compared to monotherapy during a second year of treatment [51, 52].

5 Teriparatide

Teriparatide (recombinant human parathyroid hormone, rhPTH 1–34) was the first approved osteoanabolic agent for the treatment of postmenopausal women with osteoporosis, men with hypogonadal or idiopathic osteoporosis, and men and women with glucocorticoid-induced osteoporosis who are at high risk for fracture [53–55].

This drug stimulates bone formation in active remodeling sites and on surface of bone previously inactive. Specifically, it induces differentiation of preosteoblasts into osteoblasts, stimulates preexisting osteoblasts to form new bone, and decreases osteoblast apoptosis [56].

As suggested by biochemical and histological changes, teriparatide seems to increase bone formation more than bone resorption. Regarding the behavior of bone remodeling markers, those markers reflecting bone formation increase within days of starting teriparatide and reach a peak between 6 and 12 months, remaining above baseline for the 24-month treatment duration; conversely, resorption markers increase later, but also peak at 6–12 months and remain above baseline throughout 24 months, consistent with ongoing remodeling [57, 58].

In the Fracture Prevention Trial, treatment with teriparatide has been demonstrated to reduce risk for vertebral and nonvertebral fractures among women with postmenopausal osteoporosis but has not been found to reduce the risk for hip fracture, although the study was not powered for this outcome.

Particularly, treatment with teriparatide 20-μg/day reduced the overall relative risk of vertebral and non-vertebral fractures by 65% and 53%, respectively, compared with placebo after a median treatment of 19 months [59].

Afterwards, a meta-analysis by Díez-Pérez provided evidence of efficacy of teriparatide in reducing hip fractures by 56% in patients with osteoporosis treated with teriparatide compared with controls [60].

Teriparatide is administered by daily subcutaneous injection at the approved dose of 20 μg. Because its efficacy and safety have not been evaluated beyond 2 years of treatment, the use of teriparatide is limited to a period of a maximum of 24 months during lifetime [59, 61].

In a meta-analysis by Yuan, teriparatide demonstrated a significant advantage over bisphosphonates, with a 57% of relative risk reduction in the incidence of vertebral fractures. Furthermore, compared with bisphosphonates, teriparatide treatment has been found to be associated with a significant greater improvement in BMD in lumbar spine at 6 months, 12 months, and 18 months and in femoral neck at 18 months [56].

When teriparatide is given to patients previously treated with bisphosphonates, a slower response in terms of BMD increase has been seen [62, 63].

The transition from denosumab to teriparatide deserves particular attention, since in the first 6 months of switch, there is a rapid decline in lumbar BMD, with concurrent gradual bone loss at the hip and distal radius [52, 64].

Combination treatment, particularly with denosumab, showed higher improvement in spine and hip BMD values than monotherapy, but there are no available data on the effect of combination therapy on fracture risk [65].

A potential adverse event resulting from teriparatide treatment is hypercalcemia and related symptoms such as nausea, dizziness, arthralgia, and leg cramps. Increased 24-h urinary calcium excretion and serum uric acid, reduced serum magnesium represent other side effects important to recognize but they are rarely responsible for interruption of treatment [59]. For patients developing an increase in serum and urinary calcium, a reduction in the intake of calcium is suggested [64, 66].

Because studies in rodents showed that teriparatide increased the incidence of osteosarcoma, this drug originally carried a black box warning about risk for osteosarcoma.

An additional warning exists for subjects with an unexplained persistent elevation of alkaline phosphatase, because of the potential for Paget's disease, which is a condition associated with a higher risk of developing osteosarcoma. Nevertheless, a postmarketing surveillance study has not observed a connection between teriparatide treatment and osteosarcoma in humans [61, 67]. In clinical practice, the history of any cancer in the past 5 years represents a contraindication to the use of PTH 1–34, because of the possible presence of PTH receptors in malignant cells [64].

Candidates for teriparatide treatment include patients who have had a major osteoporotic fracture while receiving bisphosphonates and treatment-naive persons with a history of more than two major osteoporotic fractures or a single vertebral or hip fracture and concomitant very low BMD T-scores (≤ -4) [68]. The Endocrine Society guidelines published in 2020 recommended teriparatide as the first-line therapy in patients at very high risk of fractures, such as those with severe osteoporosis (T-score < -2.5 and fractures) or multiple vertebral fractures [3].

In women and men with glucocorticoid-induced osteoporosis, the effect of teriparatide has been investigated in comparison with alendronate: a greater improvement in BMD and fewer vertebral fractures were observed in subjects receiving teriparatide than in those treated with alendronate [58].

Use of an antiresorptive agent is recommended after discontinuation of teriparatide to maintain the BMD gain, although there is not yet evidence to determine how long this follow-on treatment should be continued [3, 58].

6 Abaloparatide

Abaloparatide, a human parathyroid hormone peptide analog that is administered by daily subcutaneous injection, was approved by the FDA in April 2017 for treatment of postmenopausal women with osteoporosis who are at high risk for fracture. Although abaloparatide demonstrated a lower incidence of hypercalcemia than teriparatide, its registration was denied in Europe because of concerns about its effectiveness in reducing nonvertebral fractures, and increases in heart rate and palpitations [69].

7 Romosozumab

Romosozumab is a humanized monoclonal antibody and potent osteoanabolic agent with a dual effect on bone turnover, since it is responsible for enhancing bone formation and reducing bone resorption by blocking the sclerostin pathways. Sclerostin is a cytokine that is mainly produced by osteocytes and encoded by a gene called SOST, that has been found to regulate bone turnover by inhibiting osteoblastogenesis and bone formation by blocking the Wnt signaling pathways, which play a crucial role in bone formation and morphogenesis. Therefore, the net effect of sclerostin inhibition is decreased bone resorption and increased bone formation [70, 71].

In the FRAME (FRActure study in postmenopausal woMen with ostEoporosis) study, 1-year treatment with romosozumab led to a bone mineral density gain of 13.3% in the lumbar spine and 6.9% at the total hip from baseline and resulted in 73% lower risk of vertebral fracture and 25% risk reduction of nonvertebral fractures compared with placebo [72].

This drug, approved by the FDA in 2019, is recommended by the updated guidelines of the Endocrine Society in the treatment of women with severe postmenopausal osteoporosis and at very high risk of fracture (defined as T-score less than −2.5 and a prior fracture) or with a history of multiple vertebral fractures. It should be given at the dosage of 210 mg monthly for up to 1 year to reduce the risk of vertebral, hip, and nonvertebral fractures. Romosozumab has been demonstrated to significantly decrease the incidence of vertebral fractures at 12 months, nonvertebral fractures at 24 months, and the risk of falls at 36 months. Its use is also associated with improved bone mineral density at lumbar spine, total hip, and femoral neck [3, 73].

When compared with alendronate, a lower risk of new vertebral fracture and clinical fractures at the 12th month was observed [74].

Romosozumab increases bone formation markers (like procollagen type 1 amino-terminal propeptide) and reduces bone resorption markers (such as carboxy-terminal collagen crosslinks). Considering changes in bone turnover markers, romosozumab treatment has been found associated with a marked initial gain in bone formation and a more prolonged decrease in bone resorption in contrast with treatment with PTH receptor agonists (teriparatide and abaloparatide), where both P1NP and serum CTX are elevated as expression of the concomitant stimulation of bone formation and absorption. This suggested a larger osteoanabolic window for romosozumab compared with PTH analogs [75].

Compared with teriparatide, romosozumab had better effectiveness in the treatment of postmenopausal osteoporosis, especially in increasing the BMD of lumbar spine, total hip, and femoral neck, decreasing the incidence of injection-site reaction [69].

Once the course of Romosozumab is completed, an antiresorptive therapy should be started in order to maintain BMD gains and reduce future risk of fracture [73].

Romosozumab used before antiresorptive medications is associated with more significant bone mineral density increases compared with the reverse sequence. When antiresorptive agents are used before romosozumab, bone density gain from romosozumab treatment is attenuated [76].

The FRAME study showed that the addition of 2 years denosumab to 1-year romosozumab treatment is similar in terms of BMD increase compared with around 6–8 years of denosumab therapy alone [77].

Romosozumab treatment is generally well tolerated with 4%–5% of patients having injection site reactions, but it carries a black box warning because of some cardiovascular safety concerns. The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) study observed the increased rates (2.5% vs. 1.9%) of adjudicated serious cardiovascular adverse events in the romosozumab group compared with alendronate group, especially cardiac ischemic events and cerebrovascular events [78]. Therefore, as per FDA, it should not be initiated in patients with myocardial infarction or stroke in the preceding year. As perer EMA, Romosozumab is contraindicated in patients with history of myocardial infarction or stroke.

However, the risk of cardiovascular disease with romosozumab is unclear, since the number of severe cardiovascular events in the trials was low, as they were not powered to assess cardiovascular outcomes [79]. Animal studies of romosozumab have not found adverse cardiovascular effects, but it has been suggested that sclerostin might inhibit vascular calcification [5]. The role of Wnt–β-catenin signaling pathway in vascular calcification and cardiovascular remodeling and the ability of romosozumab to activate Wnt may partially explain the adverse events in romosozumab receivers [80].

Possible explanations for the increased cardiovascular risk in the ARCH trial include an actual increased risk of cardiovascular events with romosozumab but also cardioprotective effects of alendronate.

Ultimately, a prudent approach is required when using romosozumab, and it is better to avoid use of this drug in patients at high cardiovascular risk until further data about its safety are available [79, 81].

8 Raloxifene and Bazedoxifene

Raloxifene, as a selective estrogen receptor modulator (SERM), exhibits tissue-specific actions. Concerning bone tissue, it acts as an agonist of the estrogen receptor to decrease bone resorption and restore the imbalance of bone turnover that is characteristic of postmenopausal estrogen deficiency (excessive resorption vs. formation). It is effective in increasing lumbar spine BMD and reducing the risk for vertebral fractures in postmenopausal women with osteoporosis but has no effect on risk for nonvertebral fractures [82].

Raloxifene does not exert an agonistic activity on mammary or uterine endometrial tissue [83]. Thus, its long-term use is associated with decreased risk for breast cancer among women at higher risk for this condition, but it is responsible for increased risk for venous thromboembolic events [84]. Other adverse effects include hot flushes, leg cramps, breast pain, and vaginal bleeding [85].

Bazedoxifene is a third-generation SERM that has shown to prevent the incidence of vertebral fractures with a similar efficacy as raloxifene, but it can also reduce the occurrence of nonvertebral fractures among high-risk women (with a femoral neck BMD T-score < -3.0 and/or ≥ 1 vertebral fracture) [86]. Like all other SERMs, it is contraindicated in presence of a history of coagulation disorders because of the increased risk of venous thromboembolism [87].

According to Komm et al., bazedoxifene may be considered a first-choice treatment in younger women at increased risk of fracture, particularly those who are likely to remain on therapy for many years and may be concerned about the long-term safety of bisphosphonates [88].

Additionally, a combination formula of bazedoxifene and conjugated estrogens was approved in 2014 for the treatment of moderate-to-severe vasomotor symptoms and the prevention of osteoporosis in postmenopausal women with a uterus [89].

9 Strontium Ranelate

It acts as a dual agent on bone remodeling by stimulating bone formation through a positive action on osteoblast proliferation and differentiation and by decreasing bone resorption through the inhibition of the recruitment and activity of osteoclasts [90].

Treatment with strontium ranelate was associated with an increase in serum bone-specific alkaline phosphatase and a decrease in serum C telopeptide cross-links of type I collagen, as well as with changes in intrinsic bone tissue quality that lead to an improvement in bone microarchitecture and strength [91–93].

As concerns its cardiac safety, strontium ranelate is contraindicated in case of uncontrolled hypertension, established, current or past history of ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease [94]. Other side effects include gastrointestinal discomfort, diarrhea, nausea, dermatitis, eczema, headache, seizure, and memory loss [95].

Thus, its prescription is now restricted and indicated only in patients with severe osteoporosis and concomitant intolerance or contraindication or serious adverse reactions to other antiresorptive drugs, a setting in which this treatment maintains antifracture efficacy with a positive benefit-risk balance [96].

Questions for Self-Assessment

1. *Which of the following osteoporosis medications exerts a dual action (bone formation and antiresorption)?*

   (a) Alendronate
   (b) Denosumab
   (c) Teriparatide
   (d) Romosozumab

   → *Correct answer:* (d)
2. *Which osteoporosis drug may offer particular benefit in diabetic patients with low bone turnover and impaired osteoblast function?*

   (a) Bisphosphonates
   (b) Teriparatide
   (c) Calcium and vitamin D alone
   (d) Denosumab

   → *Correct answer:* (b)
3. *What is a potential concern with denosumab in patients with diabetes and renal insufficiency?*

   (a) Risk of hypercalcemia
   (b) Increased bone turnover
   (c) Risk of hypocalcemia
   (d) Gastrointestinal intolerance

   → *Correct answer:* (c)

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New Antidiabetic Drugs: Effects on Bone

Emanuela Orsi and Veronica Resi

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Chapter Introduction: What You Will Learn in This Chapter
This chapter explores the intricate relationship between diabetes, particularly type 2 diabetes mellitus (T2DM), and bone health. It highlights the emerging understanding of bone fragility as a serious complication of diabetes and discusses how the disease alters bone turnover, mineral density, and overall skeletal structure. You will learn about the mechanisms behind diabetic bone disease, which includes osteoporosis and fractures, and how these are influenced by chronic hyperglycemia. The chapter also covers the effects of modern antidiabetic medications, including Sodium-Glucose Co-transporter-2 Inhibitors (SGLT2i) and Glucagon-Like Peptide 1 Receptor Agonists (GLP1RA), on bone metabolism, with a focus on their potential impact on fracture risk and bone health.

Key Points
- The effect of diabetes on bone strength and turnover.
- The role of hyperglycemia in bone fragility.
- The influence of innovative diabetes treatments (SGLT2i, GLP1RA) on bone metabolism.

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- The risk of fractures in diabetic patients and the management of diabetic bone disease.

This chapter connects with the broader context of the book by addressing the intersection of diabetes management and bone health, emphasizing the need for multidisciplinary approaches to patient care.

Learning Objectives
By the end of this chapter, you should be able to:

- Understand the relationship between type 2 diabetes and bone health.
- Recognize the mechanisms through which diabetes affects bone metabolism and increases fracture risk.
- Assess the potential impact of SGLT2 inhibitors and GLP1 receptor agonists on bone health.
- Critically evaluate current research on bone fragility in diabetic patients and the role of modern antidiabetic drugs in managing this complication.

Definitions
- *Type 2 Diabetes Mellitus (T2DM)*: A chronic condition characterized by high blood sugar levels due to insulin resistance and impaired insulin secretion.
- *Bone Mineral Density (BMD)*: A measurement of the amount of minerals (such as calcium) in a defined area of bone, used to assess bone strength and risk for fractures.
- *Osteoporosis*: A condition in which bones become weak and brittle, increasing the risk of fractures, often linked to a decrease in bone mass.
- *Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i)*: A class of drugs used to lower blood sugar levels in patients with diabetes by preventing the reabsorption of glucose in the kidneys.
- *Glucagon-Like Peptide 1 Receptor Agonists (GLP1RA)*: Medications that mimic the action of GLP-1, a hormone that regulates blood sugar and insulin levels, and may have effects on weight and bone metabolism.
- *Fibroblast Growth Factor 23 (FGF23)*: A hormone involved in phosphate metabolism and bone mineralization, which is regulated by SGLT2 inhibitors.
- *Osteoblast*: A type of bone cell responsible for bone formation.
- *Osteoclast*: A type of bone cell responsible for the resorption of bone tissue.
- *Sclerostin*: A protein that inhibits bone formation, which is regulated by GLP1.

1 Diabetes and Bone Health

In recent decades, research has focused on the relationship between diabetes mellitus and bone health. In type 2 diabetes mellitus (T2DM) there are several changes in bone strength, bone turnover, and stem cell differentiation that result in altered bone mineral density (BMD) and bone structure. Specifically, bone in these patients has an increased BMD at the femoral neck, hip, and spine, along with decreased overall bone turnover [1].

Bone fragility is now considered a real complication of T2DM: diabetic bone disease or diabetes-induced osteoporosis, causes an increased risk of fracture, with muscle-related abnormalities up to diabetic sarcopenia. Chronic hyperglycemia represents the central point of the alterations that cause bone fragility, such as alterations in the immune, vascular, and muscoloskeletal systems [2].

The co-occurrence of T2DM and osteoporosis is associated with poorer health outcomes, so it's important that they are properly recognized and managed. Patients with T2DM have a 19% increased risk of any fragility fracture and higher postfracture mortality than the nondiabetic population [3].

Furthermore, the prevalence of vertebral fractures is increased in poorly compensated and complicated T2DM, suggesting a link between bone health, glycometabolic compensation, and chronic complications [4].

Due to what has been described, it is important to evaluate the effects of innovative antidiabetic drugs on bone.

2 Sodium-Glucose Co-transporter-2 Inhibitors (SGLT2 i) and Bone

Actually, there is no clear evidence on the effect of SGLT2 i on bone metabolism and fracture risk in T2DM. The mechanisms hypotesized to explain the effect of SGLT2 i on bone metabolism are explained below.

SGLT2 i inhibit sodium and glucose cotransporter and enhanced phosphate transport via the sodium-phosphate co-transporter in the renal proximal tubules. Sodium loss would result in increased phosphate resorption and urinary calcium excretion. Fibroblast Growth Factor 23 (FGF23), which regulates systemic phosphate homeostasis and vitamin D metabolism, could be stimulated by higher serum phosphate concentrations. Consequently, an increase in FGF23 leads to phosphaturia and inhibits the production of 1,25-dihydroxyvitamin D to maintain phosphate balance. A decrease in 1,25-dihydroxyvitamin D concentrations reduces calcium absorption from the gastrointestinal tract, which is likely to affect skeletal mineralization. The reduction in calcium concentration due to urinary calcium excretion leads to the development of secondary hyperparathyroidism, stimulating parathyroid hormone (PTH) secretion. SGLT2 i may indirectly increase bone turnover through weight loss, and lowering blood glucose also may also improve bone metabolism impairment in diabetes.

A recent review focused on the effects of SGLT2 inhibitors on some aspects of bone metabolism [5]. The authors analyzed the possible mechanisms of action of the glyphozines on bone turnover, bone architecture, BMD, and calcium-phosphorus metabolism. In particular, some studies in animal models and humans report different modes of action, depending on the molecule analyzed: canagliflozin and ertugliflozin could increase bone resorption while dapagliflozin and empagliflozin seem to have no effect.

Another recent meta-analysis looked at the results of 20 randomized controlled trials, involving around 13.000 subjects. In particular, it looked at the risk of fractures in people treated with SGLT2 i compared with placebo [6].

The results suggest that the risk of fracture was not significantly different between SGLT2 i and controls. To explore the potential influence of SGLT2 i on fracture risk, several markers of bone metabolism were included in the analysis as outcome measures: CTX, procollagen type I N-terminal propeptide (P1NP), PTH, calcium, and phosphate. In five trials, there was no significant difference in CTX levels between the treatment group receiving SGLT2 i and the placebo group. Similarly, there were no significant changes in PTH, calcium, or phosphate and P1NP levels. As there was a high level of heterogeneity in CTX values, a subgroup analysis was performed to investigate the potential source of bias, and it was concluded that the trials were few and included a limited number of subjects, so it is not possible to make significant interpretation.

Finally, four trials analyzed the percentage of change in BMD at different skeletal sites, including the lumbar spine, femoral neck, total hip, and distal forearm. The results showed that there were no significant differences in BMD between patients treated with SGLT2 i and placebo. However, due to the limited number of trials and inconsistent data, the results may not be conclusive.

3 Glucogon Like Peptide 1 Receptor Agonist (GLP1 RA) and Bone

As already discussed for SGLT 2 i, the effect of GLP1 Ras on bone and fracture risk in T2DM is not completely clarified.

The mechanisms hypotized to explain the effect of GLP1 RA on bone metabolism are discussed below.

GLP1 plays an important role in the balance between osteoblast and osteoclast functions. GLP1 induces the differentiation of mesenchymal stem cells into osteoblasts, through the mitogen-activated protein kinase (MAPK) pathway. Osteocytes, produce sclerostin, which is inhibited by GLP1. Normally, stimulated osteoblasts produce macrophage colony-stimulating factor, receptor activator of nuclear factor kappa-B ligand (RANKL), and osteoprotegerin, which stimulate osteoclast precursors to maintain bone formation balance (i.e., osteoblast and osteoclast functions remain balanced). GLP1 induces MAPK and osteoblast function and inhibits osteoclast function through the calcitonin-dependent pathway [7].

In a recent metanalysis of clinical trials, the authors evaluated the effect of GLP1 RA on bone fractures in subjects with type 2 diabetes. Twenty-eight studies were included, and the results showed that the use of GLP-1Ra did not modify the risk of bone fracture in these patients, compared with the use of other antidiabetic drugs [8].

In a randomized control trial of obese women on a low-calorie-diet, participants were randomized to treatment with or without liraglutide (1.2 mg/d) for 52 weeks,

to investigate the role of GLP-1 RA on bone formation and bone mass reduction induced by weight loss. The results showed that the treatment with GLP-1 RA increased bone formation by 16% and prevented bone loss after a 12%, weight-loss induced by a low-calorie diet [9].

As previous studies have suggested that GLP-1RAs may increase bone formation and have a neutral or beneficial effect on fracture risk, Hansen MS and colleagues designed a randomized, placebo-controlled, double-blinded phase 2 study to assess the effect of semaglutide in adults at increased risk of fracture. In particular, they used procollagen type I N-terminal propeptide (PINP) as a marker of bone formation. The results showed that once weekly semaglutide did not increase bone formation in adults at increased risk of fracture, based on the bone formation marker P-PINP. The observed increase in bone resorption in the semaglutide group may be explained by the associated weight loss [10].

In conclusion, based on the available articles, the animal studies indicate the beneficial skeletal effects of GLP1RAs in contrast to what has often been observed in human studies, showing that these agents have no effect on bone mineral density (BMD) and the turnover markers.

GLP1 was also shown not to be associated with fracture risk as compared with other anti-hyperglycemic agents.

The results showed a neutral effect of GLP1RAs on BMD. Further double-blind randomized controlled trials are needed to draw more meaningful and significant conclusions about the efficacy of GLP1RAs on BMD.

4 Comparing Innovative Diabetes Drugs and Bone Health

Although SGLT-2i have shown prominent cardioprotective and nephroprotective effects compared with placebo, there has been concern that SGLT-2i may affect bone metabolism through modulation of calcium and phosphate homeostasis, as well as the effects on weight loss. Given that damage to bone health is a relatively long-term process and can be influenced by several external factors, SGLT-2i may not have adverse effects on bone health. Conversely, it has been postulated that DPP-4i and GLP-1RA may have beneficial effects on bone health by promoting osteoblast differentiation and inhibiting osteoclast activity.

Interestingly, there have been a few papers comparing the effect of SGLT2 i and GLP1 RA on bone metabolism and fracture risk.

In a recent study, Ko and collegues evaluated the risk of fractures associated with SGLT2i vs. GLP1RA, separately, in postmenopausal individuals with type 2 diabetes. The primary outcome was total fractures, including vertebral, hip, humerus, and distal radius fractures. The authors concluded that the use of SGLT2i was associated with either a similar or lower risk of fractures than incretin-based drugs even in a population at high risk of fractures [11].

In another study, Al-Mashhadi and collegues used the Danish National Patient Registry to investigate the risk of major osteoporotic fractures with SGLT2

inhibitors compared with GLP1 RA in addition to metformin. More than 27.000 subjects were included in this study. The results showed that SGLT2 inhibitors were not associated with an increased risk of fractures compared to GLP 1 RA, confirming previous studies [12].

In conclusion, SGLT2 inhibitors and GLP1 RA have clearly demonstrated important cardioprotective and nephroprotective effects in DMT2, and represent the gold standard of therapy for these patients. Alteration of bone metabolism is a critical issue in T2 diabetes, and is considered one of the new chronic complications of the disease. Due to the mechanism of action and pleiotropic effects of these drugs, it is essential to evaluate their effects on bone. The studies currently available seem to confirm their safety in terms of bone metabolism.

However, it is more difficult to demonstrate a beneficial effect on bone because of the inconsistent results of the studies. More data are needed to verify this issue and draw definitive conclusions.

Questions for Self-Assessment

1. *Which of the following is a major consequence of type 2 diabetes mellitus on bone health?*

   (a) Increased bone turnover
   (b) Decreased bone mineral density at all sites
   (c) Increased risk of bone fractures and osteoporosis
   (d) Improved bone mineralization

   Correct answer: (c) *Increased risk of bone fractures and osteoporosis*
2. *What effect do Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) have on bone metabolism?*

   (a) They increase bone resorption and fracture risk
   (b) They have no effect on bone metabolism
   (c) They may indirectly improve bone metabolism via weight loss and blood glucose reduction
   (d) They increase bone formation directly

   Correct answer: (c) *They may indirectly improve bone metabolism via weight loss and blood glucose reduction*
3. *Which of the following statements about Glucagon-Like Peptide 1 Receptor Agonists (GLP1RA) is correct?*

   (a) GLP1RAs have a proven beneficial effect on bone mineral density and fracture risk
   (b) GLP1RAs have no effect on bone turnover
   (c) GLP1RAs promote osteoblast differentiation and inhibit osteoclast activity
   (d) GLP1RAs increase the risk of bone fractures significantly

   Correct answer: (c) *GLP1RAs promote osteoblast differentiation and inhibit osteoclast activity*

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Metformin: Glycemic and Extra-Glycemic Actions

Stefano Massarini and Livio Luzi

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Chapter Introduction: What You Will Learn in This Chapter
In this chapter, we explore the multifaceted effects of metformin, a widely used medication for type 2 diabetes, and its emerging role in a range of extra-glycemic benefits. Specifically, we will delve into its potential impact on aging, cancer prevention, and weight management. You will gain insights into how metformin modulates metabolic pathways, influences cellular processes such as oxidative stress and autophagy, and its broader effects on overall health beyond glucose regulation. This chapter also provides an understanding of how metformin's diverse mechanisms of action might contribute to its longevity-promoting and anticancer effects, as well as its potential in weight management and the prevention of diabetes.

Key Points
- The role of metformin in aging and its potential to extend lifespan.
- Mechanisms underlying metformin's anticancer properties.

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- Metformin's impact on weight management and its effect on metabolic health.
- The integration of metformin in personalized antiaging and metabolic health strategies.

This chapter connects with broader discussions on metabolic regulation and therapeutic interventions in the management of chronic conditions like diabetes, obesity, and cancer. It builds upon the fundamental understanding of how metabolic pathways influence health and disease.

Learning Objectives
By the end of this chapter, readers will be able to:

- Understand how metformin influences aging through metabolic regulation and cellular pathways.
- Identify the mechanisms through which metformin acts as an anticancer agent.
- Explain the role of metformin in weight management and metabolic health improvement.
- Recognize the potential benefits of combining metformin with other therapeutic strategies to enhance its effectiveness.
- Discuss how metformin can contribute to personalized medicine approaches for aging and metabolic disorders.

Definitions

- *AMPK (AMP-activated protein kinase)*: An enzyme that acts as an energy sensor within cells, regulating metabolic processes like glucose uptake and fatty acid oxidation.
- *Autophagy*: A process by which cells break down and recycle their own components, often involved in cellular repair and stress response.
- *ROS (Reactive Oxygen Species)*: Chemically reactive molecules that can cause oxidative damage to cellular components, playing a key role in aging and disease processes.
- *SIRT-3*: A mitochondrial deacetylase involved in regulating oxidative stress and cellular health, often activated by metabolic changes.
- *Insulin/IGF-1 Signaling (IIS) Pathway*: A key metabolic pathway that regulates growth and aging, with insulin and IGF-1 (Insulin-like Growth Factor 1) receptors playing crucial roles in cell survival and metabolism.
- *mTOR (Mammalian Target of Rapamycin)*: A protein complex that regulates cell growth, proliferation, and survival, often influenced by metabolic cues.

1 Historical Overview

Metformin, a biguanide derivative, has a rich historical background in the treatment of diabetes.

Its history is linked to *Galega Officinalis*, the herbal precursor of Metformin, also known as French Lilac or Italian fitch. The active compound responsible for lowering blood glucose was identified as galegine, or isoamylene guanidine [1].

In 1918, guanidine was reported to reduce blood glucose in animals, and during the 1920s, several mono-guanidine derivates were also shown to lower blood glucose in animals [2–6].

This discovery led to the use of galegine and synthalin (two guanidines separated by a methylene chain) for the treatment of diabetes. However, they were discontinued due to toxicity and the increased availability of insulin [3, 7–11].

In 1922, Werner and Bell synthesized metformin for the first time, identifying it as dimethylbiguanide [12].

In 1929, Hesse and Taubmann and Slotta and Tschesche reported that metformin could lower blood glucose levels in animals [13, 14].

Furthermore, biguanides were found to be less toxic than mono- and diguanidines, with metformin demonstrating the least toxicity among the various methylbiguanides tested [14].

However, due to the high doses required to achieve a modest glucose lowering effect, biguanides were not initially pursued for diabetes therapy.

In 1940s, metformin was (re)discovered during the search for an antimalarial agent. During clinical testing, it was observed to reduce blood glucose levels in patients treated for influenza [11, 15, 16]. This finding led to the development of metformin hydrochloride as an anti-influenza agent, marketed under the name "Flumamine" [3, 16].

It was only in 1956 that Jean Sterne, a French physician, translated the potential blood-glucose lowering power in therapeutic use [17]. Specifically, in his initial studies, he indicated that metformin could replace insulin in some individuals with maturity-onset diabetes and reduce insulin requirements in others. However, it could not eliminate the need for insulin in those with juvenile-onset diabetes [3]. In 1957, Sterne published a brief account of his findings [18]. He described metformin as being well tolerated, even after prolonged administration, with no evidence of toxicity. At low doses, it was hypoglycemic when administered orally, both in animals and in humans with diabetes. Later studies by Sterne further elaborated on these findings in animals [19–25].

Sterne proposed the name "Glucophage" ("glucose eater"), which was adopted by the company Aron to market metformin. He also played a prominent role in ongoing research and physician education to support the introduction of metformin into clinical practice in Europe [3].

Nevertheless, metformin initially received limited attention, as it was considered less potent than other glucose-lowering biguanides (phenformin and buformin), both of which were discontinued in the 1970s due to a high risk of lactic acidosis [26].

In the early 1990s, a renewed interest in metformin emerged thanks to a series of studies by Lipha and a group of independent clinical scientists, including Gerald Reaven, Ralph DeFronzo, and Clifford Bailey—later joined by Robert Turner and Alan Garber. These investigators collaborated with the FDA to design clinical trials, analyze the data, and assess the implications for routine clinical use in the United States [3, 27].

Metformin was finally approved by the FDA on December 29, 1994, and shortly thereafter, in 1995, pivotal trial data were published in the New England Journal of Medicine [28].

The long-term cardiovascular benefits of metformin were identified by the UK Prospective Diabetes Study (UKPDS) in 1998. This trial followed individuals newly diagnosed with type 2 diabetes who were receiving glucose-lowering treatment for over a decade. The findings redefined therapeutic strategies for type 2 diabetes, highlighting that—beyond glucose-lowering effects—metformin was associated with weight neutrality, a low risk of hypoglycemia, and potential reductions in cardiovascular events and mortality [29]. Interestingly, the reduced cardiovascular risk appeared to be largely independent of glucose-lowering efficacy. A substantial body of literature has since explored the favorable effects of metformin on both macro- and microvascular complications [30, 31]. Interrogation of large databases that captured long-term treatment of type 2 diabetes consistently confirmed the cardiovascular benefits of long-term metformin use in type 2 diabetes, and a 10-year follow-up of the UKPDS published in 2008 reaffirmed the persistence of these effects [32–34].

Sixty years after its introduction in diabetes care, metformin has become the most prescribed glucose-lowering therapy worldwide and it is now included in the World Health Organization's (WHO) list of essential medicines [35].

2 Glycemic Actions

Metformin is primarily recognized for its glycemic actions, which play a crucial role in the management of type 2 diabetes mellitus (T2DM).

It is the first-line treatment recommended by clinical guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [36, 37], supported by prospective studies [38, 39] and recent meta-analyses [40, 41].

Metformin has been used to treat T2DM since the late 1950s.

It is estimated that approximately 200 million people worldwide are currently using it, making it the most commonly prescribed oral antihyperglycemic agent, either as monotherapy or in combination with sulfonylureas or dipeptidyl peptidase-4 (DPP-4) inhibitors [42–44].

Administered orally in either immediate-release or extended-release formulations, metformin (0.5–2.5 g daily) is effective for long-term glycemic control, with significant reductions in HbA1c from baseline [42–44].

In addition, metformin is increasingly used during pregnancy for the management of gestational diabetes mellitus and in women with polycystic ovary syndrome or T2DM [45].

Metformin exerts its glucose-lowering effect primarily by decreasing hepatic glucose production through suppression of gluconeogenesis and enhancing insulin-mediated inhibition of endogenous glucose output. It also reduces intestinal glucose

absorption and may improve peripheral glucose uptake and utilization, especially in skeletal muscle and adipose tissue [46, 47].

In primary hepatocytes, metformin stimulates the AMP-activated protein kinase (AMPK) pathway, leading to a reduction in glucose production [47, 48].

However, more recent findings suggest that metformin's impact on gluconeogenesis may occur independently of AMPK activation. It interferes with mitochondrial respiration, altering intracellular ATP levels, thereby reducing the energy available for gluconeogenesis [47–50].

Another proposed molecular target is mitochondrial glycerophosphate dehydrogenase, which may also contribute to metformin's inhibition of hepatic gluconeogenesis [51].

Additional mechanisms include modulation of glucagon signaling and enhancement of glucagon-like peptide-1 (GLP-1) secretion, both of which contribute to reduced hepatic glucose production [52–54].

Emerging evidence also suggests that metformin modulates the gut microbiota, which may further contribute to its glucose-lowering effects [55].

The UK Prospective Diabetes Study (UKPDS) evaluated the benefits of metformin and its favorable safety profile. In a sub-study of UKPDS (Study 146), 753 newly diagnosed overweight patients without a history of cardiovascular disease (CVD) treated with metformin experienced a 39% reduction in myocardial infarction, a 50% reduction in coronary death, and a 41% reduction in stroke compared to those receiving conventional therapy over a 10.7-year period [38].

Metformin's actions on the gastrointestinal tract involve multiple pathways. It reduces glucose absorption in the proximal intestine, likely by enhancing enterocyte glucose utilization and increasing lactate production [56].

Although the precise mechanisms remain unclear, animal studies suggest that increased expression of GLUT2 on the enterocyte membrane may be involved.

Metformin also impacts the incretin system by stimulating GLP-1 secretion from intestinal enteroendocrine cells, thereby improving glucose homeostasis. While the mechanisms behind this increase are still debated, current evidence suggests that metformin enhances GLP-1 production rather than inhibiting its degradation by DPP-4 [57, 58].

In conclusion, metformin remains a cornerstone therapy in the management of type 2 diabetes mellitus due to its diverse and effective glycemic actions. Its ability to reduce hepatic glucose production, improve insulin sensitivity, modulate intestinal glucose handling, and influence incretin hormone secretion underscores its multifaceted role in glycemic control.

3 Extraglycemic Actions

Although metformin is primarily recognized for its role in glycemic control, it has also garnered significant attention for its extraglycemic effects, which extend beyond diabetes management.

These include modulation of gut microbiota composition, influence on aging processes, potential anti-cancer properties, and promotion of weight regulation.

As such, metformin may contribute to improved metabolic health and overall well-being, positioning it as a valuable therapeutic agent in a broader spectrum of clinical contexts.

4 Gut Microbiota

The human intestinal microbiota comprises trillions of microorganisms, predominantly bacteria and viruses, that are generally considered nonpathogenic [59, 60].

Its composition can be influenced by various environmental factors such as diet, toxins, medications, and pathogens. Among these, enteric pathogens pose the greatest risk for inducing microbial dysbiosis, as shown in animal models.

Foodborne viral infections can trigger both local and systemic inflammation, thereby altering the microbiota and compromising intestinal barrier function. This may contribute to autoimmune pathogenesis, including type 1 diabetes through T-cell–mediated destruction of pancreatic beta cells [61–63].

While metformin is primarily known for reducing hepatic glucose production via AMPK-dependent [55, 64–66] and AMPK-independent [48, 50, 51] mechanisms, increasing evidence suggests it also exerts important effects on the gastrointestinal tract [57, 67].

McCreight et al. proposed that metformin's efficacy is partly mediated through the gut, via mechanisms such as enhanced intestinal glucose uptake and metabolism, increased GLP-1 secretion, elevated bile acid exposure, and modulation of the gut microbiota [57].

Duca et al. further demonstrated that metformin activates a previously unrecognized duodenal AMPK–GLP-1 receptor–PKA–dependent neuronal pathway, which contributes to reductions in both gastric glucose release and plasma glucose levels in obesity and diabetes. Notably, duodenal AMPK activation plays a key role in mediating metformin's acute glucose-lowering effects [67].

Stepensky et al. observed that metformin's glucose-lowering effects are significantly more pronounced when the drug is administered orally rather than intravenously [68].

Despite metformin's relatively short plasma half-life (3–4 h), its glucose-lowering action persists much longer, especially following intraduodenal administration, further supporting the gut as a relevant site of action [58, 69].

In a randomized, double-blind, placebo-controlled study, Wu et al. [55] investigated the effect of metformin on gut microbiota in individuals newly diagnosed with T2DM who were also on a calorie-restricted diet.

Using metagenomics and targeted metabolomics, they assessed changes in microbiota composition and function. Moreover, by transferring fecal samples to germ-free mice and employing an in vitro gut simulator, they directly examined the interaction between metformin and gut microbiota.

They found that metformin affected metabolic pathways conserved across species from different phyla, particularly genes linked to metalloproteins and metal transporters. These findings strongly support the hypothesis that modulation of the gut microbiota contributes to metformin's antidiabetic effects [55].

5 Aging

Aging is an irreversible biological process affecting all organisms and is associated with a wide range of diseases, including infections, osteoarthritis, cardiovascular disorders, dementia, and cancer [70, 71].

Metformin's potential role in modulating aging has attracted considerable attention, particularly due to its impact on longevity and age-related diseases, primarily via the regulation of metabolic pathways.

Evidence suggests that metformin may attenuate aging by reducing reactive oxygen species (ROS) and maintaining proteostasis, largely through AMPK-dependent mechanisms [72].

In the model organism *Caenorhabditis elegans* (*C. elegans*), metformin has been shown to extend lifespan by up to 50%, offering insights into the underlying genetic and molecular pathways that contribute to its longevity-promoting effects [73].

One of the key mechanisms involves modulation of the nutrient-sensing pathways, particularly the insulin/IGF-1 signaling (IIS) axis, which includes the insulin/IGF-1 receptor and insulin receptor substrate 2 (IRS2).

Metformin inhibits this pathway, and similar downregulation of IGF receptors or IRS2 has been associated with extended lifespan in murine models [72, 74, 75].

ROS, the toxic byproducts of normal cellular metabolism, contribute to the accumulation of molecular damage, including oxidative damage to DNA, proteins, and lipids, which is strongly linked to aging and degenerative diseases [71].

Metformin may mitigate ROS-mediated damage via upregulation of SIRT-3, a mitochondrial deacetylase involved in the control of oxidative stress. Karnewar et al. demonstrated that SIRT-3 knockdown led to increased oxidative stress and early cellular senescence, while metformin-induced AMPK activation enhanced H3K79 methylation, which in turn elevated SIRT-3 expression [76].

Additionally, recent studies suggest that metformin's effects on aging may extend beyond metabolic modulation. For example, in human osteosarcoma cells, metformin significantly inhibited tumor growth by inducing cell cycle arrest and promoting programmed cell death (PCD).

This effect was mediated through the ROS-dependent JNK/c-Jun signaling pathway, and inhibition of autophagy further amplified metformin-induced apoptosis. These findings suggest a role for metformin in tumor suppression, independent of the AMPK pathway [77].

In summary, while the exact mechanisms by which metformin influences aging remain under investigation, it is clear that its effects on nutrient sensing, mitochondrial function, oxidative stress, and cellular signaling may collectively contribute to enhanced health span and reduced incidence of age-associated diseases.

Future strategies should focus on large-scale, longitudinal studies to evaluate the long-term impact of metformin on aging and age-related conditions.

Combining metformin with lifestyle modifications or other pharmacological agents may offer a synergistic approach to personalized antiaging interventions based on individual genetic, epigenetic, and phenotypic profiles.

6 Cancer

Metformin has also emerged as a potential anticancer agent, with both preclinical and clinical studies suggesting its role in cancer prevention and therapy.

Epidemiological evidence shows that diabetic patients treated with metformin exhibit a lower incidence of various malignancies, including breast, colorectal, and pancreatic cancers [78].

The anticancer effects of metformin appear to be mediated through both direct and indirect pathways involving metabolic regulation.

Directly, metformin activates AMPK, which inhibits the mammalian target of rapamycin (mTOR) pathway, leading to impaired protein synthesis and reduced cell proliferation [79, 80].

AMPK activation also induces p53 phosphorylation, contributing to inhibition of invasion and metastasis [81]. Interestingly, metformin can also inhibit mTORC1 via AMPK-independent mechanisms, further amplifying its anticancer potential [82, 83].

Beyond cancer cell-intrinsic effects, metformin may influence the tumor microenvironment. For instance, metformin-induced metabolic reprogramming can alter oxygen availability in tumor tissues, thereby downregulating HIF1-driven endothelial cell proliferation.

Moreover, by lowering the energy charge in cancer cells, metformin enhances PD-L1 degradation, which boosts cytotoxic T-cell activity and antitumor immune responses [84].

In summary, while the precise molecular pathways are still being elucidated, current data suggest that metformin exerts multifaceted antitumor effects—both by inhibiting tumor growth and by modulating the immune and metabolic landscape of the tumor microenvironment.

This positions metformin as a promising adjunct in cancer prevention and treatment strategies, especially in patients with metabolic disorders.

7 Weight Management

Metformin's impact on weight management is one of its most notable extraglycemic effects, particularly relevant for individuals with type 2 diabetes.

A recent systematic review and meta-analysis conducted by Haber et al. [85] investigated the effects of metformin on weight and metabolic parameters in individuals with obesity. The analysis revealed that metformin administration resulted in a significant reduction in body weight and BMI among obese patients compared with placebo (mean difference −0.56, −0.74, −0.37 kg/m^2; $p < 0.0001$), at doses ranging from 500 to 2550 mg/day. A particularly notable percentage reduction in BMI of −2.53% was observed at the 1700 mg/day dose.

The review published in 2019 by Yerevanian et al. [86] further explored the mechanisms through which metformin facilitates weight loss and improves metabolic regulation in individuals with obesity. Metformin enhances peripheral insulin sensitivity, promoting glucose uptake and utilization in peripheral tissues and thereby reducing hyperinsulinemia and the associated propensity for weight gain. Moreover, it may regulate appetite by modulating gut-derived hormones such as GLP-1 and PYY [53, 87, 88]. Changes in gut microbiota composition have also been proposed as a contributing mechanism, alongside the activation of AMP-activated protein kinase (AMPK), which enhances fatty acid oxidation and reduces lipid accumulation [86, 89].

Metformin is also known for its role in delaying or preventing the onset of type 2 diabetes in individuals with impaired glucose tolerance (IGT). The landmark Diabetes Prevention Program (DPP) study by Knowler et al., published in the New England Journal of Medicine in 2002 [90], evaluated the efficacy of lifestyle intervention and metformin in reducing the incidence of type 2 diabetes in high-risk individuals. In this randomized controlled trial, 3234 nondiabetic participants with elevated fasting and post-load glucose concentrations were assigned to placebo, metformin (850 mg twice daily), or an intensive lifestyle intervention aimed at achieving ≥7% weight loss and ≥150 min of physical activity per week. The lifestyle intervention reduced the incidence of diabetes by 58%, while metformin reduced it by 31% compared to placebo. Although lifestyle modification was more effective, the study demonstrated that both strategies are valuable options for diabetes prevention, particularly in individuals at high metabolic risk.

Additionally, Seifarth et al. [91] investigated the efficacy of metformin in promoting weight loss among nondiabetic individuals with obesity. Their findings showed that metformin treatment led to significant reductions in body weight compared with placebo. Beyond weight loss, metformin improved insulin sensitivity and lipid profiles, indicating a broader metabolic benefit. These results suggest that metformin may be a useful therapeutic strategy for obesity management, particularly in individuals who exhibit suboptimal response to lifestyle interventions alone.

In addition to its primary function in glycemic regulation, metformin exerts a wide range of extra-glycemic effects, including facilitation of weight management, potential anticancer properties, modulation of aging-related pathways, and favorable alterations of the gut microbiota. These actions collectively contribute to improved metabolic health and potentially extended longevity.

Future strategies to optimize the benefits of metformin should include the exploration of combination therapies with other pharmacological agents or lifestyle-based interventions. Personalized medicine approaches tailored to individual

genetic, epigenetic, microbiome, and metabolic profiles may enhance treatment efficacy. Furthermore, large-scale, long-term clinical trials are warranted to better understand the role of metformin in aging and to evaluate its potential to improve health span and longevity across diverse populations.

Questions for Self-Assessment

1. *What is the primary mechanism through which metformin influences aging?*

   (a) By inhibiting mTOR activity
   (b) By reducing reactive oxygen species (ROS)
   (c) By directly activating SIRT-3
   (d) By increasing IGF-1 signaling

   Correct answer: (b) By reducing reactive oxygen species (ROS)
2. *Which of the following cancers has been shown to have reduced incidence in diabetic patients treated with metformin?*

   (a) Brain cancer
   (b) Colorectal cancer
   (c) Liver cancer
   (d) Lung cancer

   Correct answer: (b) Colorectal cancer
3. *How does metformin assist in weight management?*

   (a) By promoting fat storage in the liver
   (b) By increasing insulin resistance
   (c) By modulating gut-derived hormones like GLP-1 and PYY
   (d) By inhibiting the production of glucose in the liver

   Correct answer: (c) By modulating gut-derived hormones like GLP-1 and PYY

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Further Reading/References

For readers interested in deepening their knowledge of metformin and its broader therapeutic roles, the following references provide additional insights into its effects on aging, cancer, and metabolic health:

Cejuela M, Martin-Castillo B, Menendez JA, Pernas S. Metformin and breast cancer: where are we now? Int J Mol Sci. 2022;23(5):2705. https://doi.org/10.3390/ijms23052705. PMID: 35269852; PMCID: PMC8910543.

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Insulin and Bone

Renato Diana and Livio Luzi

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Chapter Introduction: What You Will Learn in This Chapter
This chapter explores the intricate relationship between insulin and bone metabolism, a crucial topic for understanding bone health in patients with diabetes. Insulin, traditionally known for its role in regulating glucose metabolism, also plays a significant role in bone homeostasis, influencing bone growth, turnover, and repair. This chapter will detail how insulin impacts the skeleton, both in type 1 and type 2 diabetes, and discuss the implications for bone density, fracture risk, and bone quality.

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Key Points

- The *biological role of insulin* in bone cells, particularly osteoblasts, osteoclasts, and osteocytes.
- How *insulin resistance* and *hyperinsulinemia* contribute to altered bone metabolism in diabetic patients.
- The effects of *insulin therapy* on bone health, especially in patients with type 1 and type 2 diabetes.
- The potential *mechanisms linking insulin signaling* with bone remodeling.
- The role of insulin in *bone mineralization* and its interaction with other metabolic pathways that influence bone density and fracture risk.

This chapter ties into the broader context of metabolic diseases and bone health presented in the book, providing essential information for understanding the complex relationship between insulin and bone metabolism.

Learning Objectives

By the end of this chapter, you should be able to:

- Describe the role of insulin in regulating bone metabolism.
- Understand the impact of insulin resistance and hyperinsulinemia on bone health.
- Evaluate how insulin therapy influences bone density and fracture risk.
- Identify the molecular mechanisms linking insulin signaling to bone remodeling.
- Assess the clinical implications of insulin in managing bone-related issues in diabetic patients.

Definitions

- *Insulin*: A hormone produced by the pancreas that plays a critical role in regulating blood glucose levels. It also affects bone metabolism by influencing the activity of osteoblasts, osteoclasts, and osteocytes.
- *Osteoblasts*: Bone-forming cells responsible for the synthesis of bone matrix and mineralization. Insulin can promote osteoblast differentiation and function.
- *Osteoclasts*: Cells involved in the resorption of bone tissue. Insulin resistance may increase osteoclast activity, leading to bone loss.
- *Osteocytes*: Mature bone cells embedded within the bone matrix that play a crucial role in regulating bone remodeling and responding to mechanical stress. Insulin affects their function in the context of bone health.
- *Bone Remodeling*: A continuous process involving the resorption of old bone by osteoclasts and the formation of new bone by osteoblasts. Insulin plays a role in regulating this process.
- *Insulin Resistance*: A condition in which the body's cells become less responsive to insulin, often leading to increased blood glucose levels and altered bone metabolism in diabetic patients.

1 Introduction

Insulin is a peptide hormone produced and secreted by beta-cells located in the pancreatic islets of Langerhans [1]. It is essential for glucose metabolism and for maintaining blood glucose levels within a physiological range by reducing its concentration in the bloodstream. Its synthesis and secretion are stimulated by glycemia itself [2]. Insulin acts on target organs by binding to insulin receptors (IR) located on the cell membranes of various cell types. IR is a tyrosine kinase receptor, and its activation triggers an intracellular signaling cascade that regulates several cellular functions [3].

Insulin primarily acts on three types of cells:

- Hepatocytes, where it promotes glucose uptake into cells via GLUT2 transporters. It stimulates glycogen synthesis (a form of glucose storage) and inhibits glucose production (glycogenolysis and gluconeogenesis). It also stimulates lipogenesis, which is the conversion of carbohydrates into lipids [4].
- Myocytes, where it promotes protein synthesis and glucose uptake into cells via GLUT4 transporters. In myocytes, glucose is used as an energy source or stored as glycogen [5].
- Adipocytes, where it promotes glucose uptake into cells via GLUT4 transporters. It inhibits lipolysis, the breakdown of stored fats in adipocytes, and stimulates lipogenesis in this tissue as well as in the liver [6].

In recent decades, the action of insulin on bone has been increasingly studied, as well as the influence of bone on glucose metabolism. In fact, the skeletal system is not an inert structure with only a support and protection function, it also acts as an endocrine organ.

2 Bone and Diabetes

To understand the interactions between insulin and bone, it is useful to evaluate the structural changes that occur in the bones of patients affected by diabetes.

Both type 1 diabetes (T1D)—characterized by insulin deficiency—and type 2 diabetes (T2D)—generally associated with hyperinsulinemia, except in advanced stages)—are associated with an increased risk of fractures, along with alterations in bone microarchitecture and new bone formation [7–13]. These findings do not correlate directly with changes in bone mineral density (BMD) that occur in the presence of these two main types of diabetes. In fact, in T1D, BMD is reduced [14–19], whereas in T2D, BMD is often preserved or even increased [20, 21]. Furthermore, in T1D, the fracture risk is significantly higher than what would be expected based on the reduction in BMD [22] alone, suggesting that BMD is not the only parameter influencing fracture risk in diabetic individuals.

Several studies have shown that insulin therapy itself increases fracture risk in diabetic individuals [23], with a 38% higher risk compared to patients treated with oral antidiabetic drugs alone [24]. One explanation is the elevated risk of hypoglycemic episodes, which can lead to falls, in patients receiving insulin therapy [9, 25, 26]. This increased risk may be further amplified by various diabetes-related complications, particularly in advanced stages of the disease when insulin therapy is more frequently used. Neuropathy, for instance, can impair awareness of hypoglycemia, disrupt gait, and reduce sensitivity in the lower limbs, all of which elevate the risk of falls [27, 28]. Retinopathy may also contribute by impairing vision [29], while microvascular disease [30] and nocturnal urination (nycturia), which fragments sleep and may lead to nighttime falls, are additional contributing factors [31].

There are other factors in diabetes that impact bone health. The hyperglycemia present in diabetes increases adipogenesis, which in turn reduces BMD by itself [32]. Advanced glycation end products (AGEs) have harmful effects on the skeleton, affecting both blood vessels and the extracellular matrix. In vitro, AGEs increase the production of sclerostin by osteocytes, which negatively regulates bone formation via WNT signaling inhibition and suppression of osteoblast differentiation [33–35].

2.1 Type 1 Diabetes

Here below is a more specific overview of the bone changes in T1D.

As previously mentioned, in T1D, BMD is reduced. In particular, there is a reduction in BMD both in femoral neck and lumbar spine [8, 36]. Bone turnover markers such as bone-specific alkaline phosphatase (ALP), C-telopeptide, and osteocalcin are also reduced [37–39]. C-peptide levels, a marker of endogenous insulin secretion, positively correlate with BMD at both sites in both diabetic and nondiabetic individuals [40, 41], confirming insulin's role in bone metabolism [42].

Interestingly, lumbar BMD is lower in patients with acute-onset T1D compared to slow-progressor T1D, despite the younger age of the former group. This suggests that decreased insulin secretion has a greater impact on BMD reduction than age alone [43]. This difference between acute-onset and slow-progressor T1D has not been observed for the femoral neck. Moreover, there is evidence suggesting that the reduction in BMD in individuals with T1D occurs no earlier than 2 years after the onset of the disease [44] but still within a few years of the onset of T1D [45–47].

For example, Gunczler et al. [45] found a significant decrease in BMD in over 50% of 26 children with T1D, with an average age of 12.1 years and a mean disease duration of 4.6 years, thus demonstrating a rapid impact on bone health. These findings have been confirmed in subsequent studies [48, 49].

In patients with T1D, various skeletal development alterations have been observed: reduced linear growth during adolescence, decreased BMD in adulthood with an increased risk of developing osteoporosis and thus fragility fractures, and poor bone healing following fractures [50]. Another interesting data point is related

to Insulin-like Growth Factor-1 (IGF-1), a growth factor structurally similar to insulin and produced by the liver in response to growth hormone (GH) stimulation. IGF-1 has anabolic effects on bone [51, 52] and its levels are lower in patients with T1D compared to controls [53].

Murine Models

In T1D mouse models, insulin increases BMD both in trabecular and cortical bone [54]. The degree of glycemic control, which is directly correlated with insulin reserve, strongly correlates with bone integrity and the speed of fracture healing [55, 56]. In long-term T1D models [57] it has been found that the bones exhibit specific mineralization defects. The major deficits in these insulin-deficient murine models are: reduced mineralized surface, decreased mineral apposition rate, reduced osteoid surface, decreased osteoblastic activity, and a reduced number of osteoblasts [58–61]. This corresponds to a depression of bone remodeling in untreated insulin deficiency. These data are supported by changes in the concentration of surrogate markers, such as Osteocalcin (OC)—an osteoblast/osteocyte-produced peptide that is a bone remodeling marker also involved in glucose metabolism [62–64]—and Deoxypyridinoline in urine (DU), a marker of bone resorption. Both OC and DU are reduced in untreated T1D [65–67]. These data are consistent with the finding of reduced bone strength in the total femur and femoral neck in type T1D mice [68, 69].

2.2 Type 2 Diabetes

In T2D, BMD is generally normal or even increased [19, 70–72], with average increase of 2–8% both at the regional level and at the whole body level [73]. However, bone microstructure and strength are compromised, increasing fracture risk [72–76]. Several studies have shown a correlation between BMD and insulin dose [77, 78] or C-peptide in the 24-h urine [77] in patients with T2D. One study has shown an increase in BMD in patients with recent onset of type 2 diabetes (T2D) compared to euglycemic controls, highlighting a positive association with hyperinsulinemia and insulin resistance [79]. These studies suggest that hyperinsulinemia may preserve and even increase BMD [80]. Another difference between T1D and T2D is observed at the biochemical level. In fact, while bone ALP is reduced in T1D [37, 38], in T2D, bone ALP levels do not differ from those of controls [81].

Insulin therapy, both in patients with T1D and in patients with T2D where there is functional exhaustion of pancreatic beta cells, seems to reverse the histological, structural, and biochemical abnormalities associated with insulin deficiency, thereby increasing bone mechanical strength [55, 56, 69].

3 Insulin Receptors

Insulin's role in bone metabolism can be evaluated by considering the localization of insulin receptors (IR) and their function. IRs are not only found in tissues primarily involved in glucose metabolism, such as the liver, muscle tissue, and adipose tissue, but also in bone tissue. Preosteoblasts and osteoblasts express different subtypes of insulin receptors, with IR-A expressed in preosteoblasts and IR-B expressed in mature osteoblasts [42]. IRs have been found in: human primary osteoblasts [42], osteoclast-like cells [82], and osteoblasts in rats [83–86]. In vitro, primary cranial osteoblasts and many osteoblast-like cell lines express a very high number of IRs on the surface and have a high capacity to bind insulin [87–89]. Insulin signaling promotes osteoblast differentiation and the expression of Osteocalcin by osteoblasts in mice [90]. In vivo, insulin signaling in osteoblasts stimulates bone formation and increases the peak BMD during growth [91]. The presence of IR is essential for the survival and proliferation of osteoblasts [91, 92]. The expression of RUNX2 (a transcription factor necessary for osteoblast maturation) is reduced in osteoblasts that do not express IR [92, 93], this is explained by the fact that insulin inhibits Twist2, which in turn would inhibit RUNX2 [91, 93]. In an in vivo model, IR knockout mice have shown reduced bone formation [94, 95]. In mosaic mice ablated for 90% of the IR, a marked growth delay has been observed [96]. IRs act on IRS substrates (from 1 to 4). IRS2 stimulates bone formation, while IRS1 regulates bone turnover [95, 97]. In IRS1-deficient mice, bone healing is impaired and is restored when IRS1 is re-expressed at the fracture site [98].

IR is also present on osteoclasts, and its activation by insulin inhibits osteoclast activity in vitro [83]. Therefore, insulin stimulates bone formation on one hand and would reduce bone resorption on the other. On the other hand, there is evidence that insulin signaling in osteoblasts promotes bone resorption, not through direct stimulation of osteoclasts, but through its action on osteoblasts, as it reduces the expression of osteoprotegerin by the osteoblasts themselves [99]. Osteoprotegerin is a glycoprotein that inhibits osteoclast differentiation, thus playing a protective role on bone [100–102].

4 Insulin as an Anabolic Agent

Insulin has anabolic effects on bone [50, 103] by stimulating osteoblast differentiation [104, 105]. In experimental models, it has been observed that insulin administration, up to hyperinsulinemia, stimulates osteoblast activity and the rate of mineral apposition [61]. In vitro, cultured osteoblasts, in response to insulin administration, increase their proliferation rate [106, 107], collagen synthesis [88, 108, 109], ALP production [110, 111] and glucose uptake [88, 108, 109]. Insulin appears to inactivate p27, a cyclin-dependent kinase inhibitor, which could otherwise suppress osteoblast proliferation [112]. Consistently, insulin deficiency in animal models is

associated with abnormalities in bone microarchitecture, which can be prevented by insulin administration [50]. As mentioned, insulin can promote bone resorption by reducing the expression of osteoprotegerin, which in turn inhibits osteoclast activity. This mechanism has been observed primarily in murine models [99, 113].

Ivaska et al. [114] conducted a study on humans to evaluate the variation in bone metabolism markers in response to insulin administration. After 4 h of insulin infusion, c-telopeptide (CTX—a bone resorption marker) decreases, total OC remains unchanged, and undercarboxylated osteocalcin (ucOC—the active form of osteocalcin) decreases. Therefore, insulin seems to have an anabolic effect as it reduces resorption, but no direct effects on osteoblasts and bone formation were found. This conflicts with what was found in mice [99, 113], where insulin stimulates bone resorption with an increase in CTX. Other studies suggest that acute variations (much less than 4 h) in insulin levels do not affect human bone metabolism [115, 116]. In summary, elevated insulin levels maintained for more than 4 h reduce bone resorption, OC, and ucOC. Acute changes (for a short period) in insulin levels do not affect bone formation in humans. It is therefore evident that insulin has an anabolic effect on bone, likely primarily through stimulation of osteoblasts. However, there is conflicting evidence regarding the effect of insulin on bone resorption.

5 Osteocalcin

Bone also plays a regulatory role in glucose metabolism, especially through the production of osteocalcin (OC) [117]. OC is a protein primarily produced by osteoblasts, but also by osteocytes and to a lesser extent by chondrocytes and adipocytes. It is secreted into the circulation during bone remodeling [118]. OC stimulates the differentiation of osteoblasts and the maturation of osteocytes, is involved in the maintenance of bone mineralization, and is considered a marker of bone remodeling [119]. In addition to this local action at the bone level, OC plays an important regulatory role in energy metabolism, acting on beta cells and adipocytes [118, 120]. The role of OC was initially studied in mice, where it was found to increase beta-cell proliferation, insulin secretion, and insulin sensitivity [121, 122]. The stimulatory effect on beta-cell proliferation in mice occurs both during the proliferative peak, which is in the perinatal phase, and in adult mice [123]. The effect on insulin sensitivity is mediated by adiponectin [124], a hormone produced by adipocytes in response to OC. Only the undercarboxylated form (ucOC) is active on the beta cells, where it regulates the activity of cyclins [121, 122, 125], and on adipocytes [122], likely through the activation of the GPRC6A membrane receptor [123, 126]. OC is stored in the bone matrix and is released during bone resorption [127, 128], during which osteoclasts secrete protons, lowering the pH of the extracellular environment at the resorptive lacuna. The reduced pH promotes the decarboxylation of OC to ucOC, which then enters the bloodstream [91, 99]. Mice lacking osteoblasts, in addition to structural bone issues, exhibit alterations in glucose metabolism (increased blood glucose, reduced insulin levels, and decreased insulin sensitivity).

The administration of OC restores blood glucose and insulin levels, but not insulin sensitivity [129]. Likely, osteoblasts have another way to regulate it, independent of OC. Similarly, OC knockout mice have insulin deficiency and impaired glucose tolerance [121], precisely because a deficiency of ucOC compromises beta cell proliferation and insulin secretion [130]. These murine models also have reduced serum levels of adiponectin, as OC stimulates adipocytes to release adiponectin [123]. Other factors highlighting the interaction between bone and glucose metabolism are periostin and RANK Ligand (RANKL). Periostin is a protein derived from osteoblasts and osteocytes. In murine models, it has been observed to enhance the regeneration of beta cells [35]. RANKL is a mediator of osteoclast differentiation, but it is also involved in the regulation of glucose metabolism. Inhibition of RANKL signaling increases hepatic insulin sensitivity and is involved in beta cell replication in mice [131]. In patients with osteoporosis, inhibition of RANKL improves insulin sensitivity [132].

The interaction between OC and energy metabolism has also been confirmed in humans. Patients with T1D and T2D have reduced levels of OC [125, 133–136]. Obese patients also have reduced levels of OC [137–139]. In addition, the serum levels of osteocalcin are negatively associated with glycemia and insulinemia in diabetic patients [140]. There is therefore a continuous reciprocal influence; as we saw earlier, insulin stimulates osteoblast proliferation and their production of osteocalcin [104, 105, 125, 141], and the latter stimulates beta cells to release insulin and increases insulin sensitivity.

In conclusion, the interaction between insulin and bone is very complex and is regulated by various factors that are not yet fully understood. Recent evidence suggests that, under normal circumstances, insulin could promote osteoblast differentiation, leading to increased osteocalcin production. This, in turn, may enhance insulin secretion from the pancreas and improve insulin sensitivity. Therefore, there is a continuous interaction between bone and glucose metabolism, with insulin playing a key role in this process.

Questions for Self-Assessment

1. *How does insulin affect osteoblast activity?*

   (a) It inhibits osteoblast differentiation
   (b) It promotes osteoblast differentiation and bone formation
   (c) It has no effect on osteoblast activity
   (d) It stimulates osteoclast activity, reducing bone formation

   Correct Answer: (b) It promotes osteoblast differentiation and bone formation

2. *Which of the following is a consequence of insulin resistance on bone health?*

   (a) Increased bone mineralization
   (b) Decreased osteoblast activity
   (c) Enhanced osteocyte function
   (d) Reduced osteoclast activity

   Correct Answer: (b) Decreased osteoblast activity

3. *What is the effect of insulin therapy on bone health in diabetic patients?*

   (a) It decreases fracture risk by promoting bone formation
   (b) It increases fracture risk by inhibiting osteoclast function
   (c) It may have a neutral or slightly negative impact on bone density
   (d) It has no impact on bone health

Correct Answer: (c) It may have a neutral or slightly negative impact on bone density

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Further Reading/References

For readers interested in exploring the topic further, the following references provide deeper insights into the role of insulin in bone metabolism:

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Thyroid and Bone

Silvio Pisano and Claudio Cusini

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Chapter Introduction: What You Will Learn in This Chapter
This chapter explores the intricate relationship between thyroid function and bone health, focusing on how variations in thyroid-stimulating hormone (TSH), as well as overt and subclinical hypothyroidism and hyperthyroidism, impact bone metabolism, bone mineral density (BMD), and fracture risk.

Readers will gain a comprehensive understanding of:

- How TSH influences bone turnover markers, BMD, and skeletal fragility.
- The pathophysiological effects of both hypothyroidism and hyperthyroidism on bone health.
- The differential impact of thyroid dysfunctions across age and sex, particularly in postmenopausal women.
- The role of subclinical thyroid disorders and thyroid hormone replacement therapy on long-term skeletal outcomes.

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This chapter links endocrine and bone health, and serves as a bridge between basic endocrine physiology and clinical management of patients at risk for osteoporosis and fragility fractures.

Learning Objectives
By the end of this chapter, readers will be able to:

- Describe how TSH and thyroid hormones affect bone turnover and BMD.
- Differentiate the skeletal effects of hypo- and hyperthyroidism.
- Recognize the clinical implications of subclinical thyroid disorders on bone health.
- Evaluate fracture risk in patients with thyroid dysfunction and understand therapeutic considerations.

Definitions
- *TSH (Thyroid-Stimulating Hormone)*: A pituitary hormone that regulates the production of thyroid hormones (T3 and T4) by the thyroid gland.
- *Bone Mineral Density (BMD)*: A measurement of the amount of mineral matter per square centimeter of bones, used as a diagnostic tool for osteoporosis.
- *Bone Turnover Markers*: Biochemical markers that reflect the rates of bone formation and resorption.
- *Subclinical Hypo-/Hyperthyroidism*: Thyroid dysfunctions characterized by abnormal TSH levels with normal circulating thyroid hormones and absence of overt symptoms.
- *Thyrotoxicosis*: The clinical state resulting from excess thyroid hormones, often due to hyperthyroidism.

1 Thyroid Hormone Receptors (TRs) in Bone

TRs are composed of three subtypes: TRα1, TRβ1, and TRβ2, which are widely distributed. TRα1 mainly exist in the cardiac and skeletal muscles, TRβ1 is mainly present in the brain, kidney, and liver, and TRβ2 is confined to the pituitary gland and hypothalamus, where it regulates TSH secretion through a negative feedback mechanism and the expression of thyrotropin releasing hormone (TRH) [1].

Of these receptors, TRβ1 and TRα1 are expressed in bone, and TRα1 is approximately ten times more present than TRβ1 [2]. TRα1 plays a predominant role when thyroid hormones (THs) are at basal concentration and TRβ1 responds rapidly to sudden THs variations.

TRs also include membrane receptors, such as monocarboxylate transporter 8 (MCT8), which mainly transports T4, MCT10, which transports T3 better, L-type amino acid transporter 1 and 2 (LAT1, LAT2) [3]. The absence of MCT8 in mice demonstrated accelerated bone turnover, resulting in impaired osteoclastogenesis, however its specific absence at the level of osteoprogenitors demonstrated increased

trabecular bone mass, suggesting that MCT may be a negative regulator of osteogenesis [4, 5].

Thyroid hormones are metabolized in skeletal cells [6]. The DIO1 enzyme is not expressed in cartilage or bone while DIO2 is expressed in osteoblasts [7]. Its activity in developing chick growth plate is limited to the perichondrium [8], indicating that this enzyme plays a role in thyroid hormone regulation and signaling during fetal bone development. The inactivating enzyme DIO3 is particularly present during development in all skeletal cell lines, with the highest activity at the chondrocyte level [7, 9]. The control of tissue availability by DIO2 and DIO3 is therefore important for skeletal development, linear growth, and osteoblast function.

1.1 Thyroid Hormones on Chondrocytes

Hypertrophic chondrocyte differentiation and vascular invasion of cartilage is sensitive to thyroid function [10]. In vitro, it has been demonstrated that T3 has the ability to inhibit cell proliferation and simultaneously stimulate hypertrophic chondrocyte differentiation and cell apoptosis [11, 12]. These effects occur through interaction with key pathways and growth factors that mediate cellular maturation. During endochondral ossification, chondrocytes go through three stages: proliferating chondrocytes, prehypertrophic chondrocytes, and hypertrophic chondrocytes, which determine the length of the bone [13]. Proliferating chondrocytes are present around the joints, while hypertrophic chondrocytes are formed by constantly moving in front of the proliferating chondrocytes themselves. Ihh (Indian Hedgehog) is an intercellular signaling molecule expressed in hypertrophic and pre-hypertrophic chondrocytes, which is part of the Hh protein family [14], which is increased at the level of the tibial epiphyses in treatment with THs [15]. Ihh stimulates the expression of PTHrP, which, through a negative feedback loop, inhibits chondrocyte maturation and stimulates chondrocyte proliferation. In this way, THs regulate the length of long bones by controlling the zone of chondrocyte maturation via the Ihh-feedback loop of PTHrp [13, 16]. Furthermore, THs promote chondrocyte differentiation and proliferation by enhancing Wnt4 activity through the removal of C-terminal amino acids mediated by carboxypeptidase Z (CPZ), which is activated by THs [17]. It has also been demonstrated how the expression of the IGF-1 receptor and chondrocyte differentiation markers (such as collagen X and ALP) is upregulated under the effect of T3, as well as the intracellular accumulation of β-catenin via the IGF1/P13k/Akt pathway [18].

Furthermore, T3 stimulates the expression of genes involved in cartilage matrix synthesis, mineralization and bone degradation, including the proteoglycan matrix [19] and collagen degradation via enzymes such as aggrecanase-2, MMP13, Wnt4, and the FGF receptor 3 (FGFR3) [20]. In summary, thyroid hormone plays a coordinating function in the progression of endochondral ossification, acts by

stimulating the genes that control the maturation of chondrocytes, and regulates the synthesis of the cartilage matrix, mineralization, and degradation [1–33].

1.2 Thyroid Hormones Effects on Osteoblasts

The consequences of T3 stimulation on different osteoblastic cell lines vary considerably depending on the species, the cell type, the anatomical origin of the osteoblasts, the stage of differentiation and the dose and duration of T3 treatment [26, 27]. Therefore, T3 is capable of determining a stimulation, inhibition, or neutral effect on the osteoblastic cell population. However, a general consensus indicates that T3 has the main function of stimulating osteoblastic proliferation and differentiation, synthesis and mineralization of bone matrix. T3 stimulates osteoblastic activity directly and indirectly via complex pathways involving many growth factors and cytokines. T3 increases the expression of osteopontin, collagen type I, osteocalcin, alkaline phosphatase, IL6–IL8, IGF1, FGFR1, which lead to the activation of MAPK signaling, as well as regulating the Wnt/b-catenin pathway [24, 25, 28]. Furthermore, it is capable of enhancing the response of osteoblasts to PTH by modulating the expression of PTH/PTHrP receptors [26].

Among the DIOs, the one most present in the osteoblastic cell population is DIO2 [7], which knockout has demonstrated greater bone mineralization and a tendency to fruiting, typical of bone manifestations in hypothyroidism [23]; therefore, DIO2 is fundamental for the correct functioning of osteoblastic activity.

1.3 Thyroid Hormones Effects on Osteoclasts

Osteoclasts express mRNA for TRα1 and TRβ1; however, it is unclear whether these receptors are functional as the sensitivity of TRs antibodies is not sufficient to detect endogenous proteins. Studies carried out on mixed cultures of osteoclast and bone marrow cell lines have given contradictory results, and it was not very clear whether the stimulus to bone resorption derives directly from the effect of T3 on the osteoclasts themselves or indirectly through molecular effects on osteoclastic cell lines [29], different cases on cell cultures have shown the implication of various cytokines and growth factors including IGF1 [30], interleukins [31], TGF-β [32], and prostaglandins as mediators of secondary responses to osteoclasts. Furthermore, in bone marrow stromal cells, the expression of RANKL, IL-6, IL-8 PGE2 was increased as well as the inhibition of OPG, consistent with an indirect activation of osteoclasts by these molecules. However, other studies on bone cell cultures have shown that the action of T3 on bone cells is particularly rapid and involves the mobilization of intracellular calcium, suggesting that the non-genomic TR-independent role could be relevant [33]. Overall, it is not

completely clear whether T3 has a direct effect in osteoclastic cell lines or whether its effects on bone resorption are secondary to the role of T3 in the remaining bone marrow cell population.

2 TSH in Bone

The expression of TSH receptor (TSHR) is detectable mainly in thyroid follicle cells, but its presence in osteoclasts, osteoblasts, and chondrocytes suggests that TSH also has a direct action on bone [34, 35]. Although TSH α and β subunits are not expressed in osteoblasts and osteoclasts, alternative TSHb variants (TSHb-sv) have been identified in the bone marrow [36, 37]. The mRNA encoding this isoform was also identified at low levels in primary osteoblasts but not in osteoclasts. However, the underlying mechanisms remain unknown as TSH did not have a proliferative or differentiating effect on osteoblasts via activation of cAMP, ERK, p38, MAPK, or AKT signaling pathways in primary osteoblasts or marrow stromal cells bone in vitro [38].

2.1 TSH Effects in Chondrocytes

The expression and function of TSHR in cartilage remain relatively unexplored. However, emerging evidence suggests a dual role. In mesenchymal stem cells, TSH has been shown to stimulate self-renewal and upregulate chondrogenic marker genes, thereby promoting chondrocyte differentiation [39]. In contrast, in mature chondrocytes, TSH signaling, mediated through cAMP activation, has been linked to decreased expression of key chondrogenic markers such as SOX9 and type IIa collagen, ultimately inhibiting chondrocyte differentiation [34]. These findings suggest that the effects of TSH on chondrocytes may vary depending on the cellular context and developmental stage.

2.2 TSH Effects in Osteoblasts

The TSHR has been identified in osteoblasts and osteoclasts, as well as in UMR106 rat osteosarcoma cells [40]. While the lack of TSH and TSHβ expression in these cells suggests a paracrine or endocrine role, the direct effects of TSH on osteoblasts remain controversial [41].

Some studies have shown that TSH can inhibit osteoblast differentiation and function by reducing the expression of key osteogenic markers like type I collagen, bone sialoprotein, and osteocalcin. This inhibition may be mediated through the Wnt signaling pathway [35]. Other studies, however, have demonstrated that TSH

can stimulate osteoblast differentiation and function, potentially through the activation of protein kinase C and noncanonical Wnt signaling [42]. Furthermore, TSH has been shown to influence osteoblast proliferation and differentiation by regulating the expression of IGF-1, IGF-2, and IGF-binding proteins [43].

Despite these conflicting findings, it is generally accepted that the physiological effects of TSH on osteoblasts are likely to be modest. The low levels of TSHR expression and the lack of a robust cAMP response in osteoblasts suggest that alternative signaling pathways may be involved [41, 44]. It is possible that TSH may exert its effects on osteoblasts indirectly, through the modulation of other hormonal factors or cytokines.

Further research is needed to fully elucidate the complex role of TSH in bone metabolism and to determine the specific mechanisms by which TSH influences osteoblast function.

2.3 TSH Effects in Osteocytes

While osteoclasts express TSHR, the direct effects of TSH on these cells are less clear. While some studies have shown that TSH can inhibit osteoclast differentiation and function, others have reported no significant effect [45].

Several studies have demonstrated that TSH can inhibit osteoclastogenesis in vitro, reducing the expression of key osteoclast markers like tartrate-resistant acid phosphatase, MMP-9, and cathepsin K. This inhibition is thought to be mediated by TNF-α, which can disrupt the activation of transcription factors such as AP-1 and NF-κB [46].

However, the relationship between TSH and TNF-α is complex. While TSH can inhibit TNF-α production in osteoclasts, it can also stimulate TNF-α production in osteoblasts [42]. This suggests a potential counter-regulatory mechanism, where TSH may inhibit bone resorption by osteoclasts while simultaneously stimulating bone formation by osteoblasts [47].

Further research is needed to fully elucidate the mechanisms by which TSH regulates osteoclast function and the potential clinical implications of these findings.

3 Impact of Thyroid Dysfunction on Skeletal Development

3.1 Hypothyroidism and Skeletal Growth

Hypothyroidism, a common endocrine disorder in children (affecting 1 in 1800 newborns), disrupts skeletal development and bone maturation. This manifests as delayed growth, shorter stature, and a delayed “bone age” on X-rays. Severe cases can lead to complete growth arrest and complex skeletal malformations [48].

Fortunately, thyroid hormone replacement therapy offers a remarkable solution. Children treated early with T4 experience a rapid "catch-up" in growth and accelerated bone maturation, highlighting the crucial role of thyroid hormones in development. However, the timing and duration of hypothyroidism before treatment can influence final adult height [49].

Studies show that most children with congenital hypothyroidism treated early achieve normal bone mineral density (BMD) and reach their predicted adult height after 8.5 years of follow-up [50, 51].

3.2 Thyrotoxicosis and Skeletal Growth

Thyroid hormone (T3) plays a vital role in regulating the growth rate of cartilage cells within the growth plates, which are responsible for bone lengthening. In contrast to hypothyroidism, childhood thyrotoxicosis (often caused by Graves' disease) leads to accelerated bone development and rapid growth [20, 52]. However, this comes at a cost. The advanced bone age leads to premature fusion of the growth plates, resulting in early cessation of growth and ultimately, short stature.

Severe cases in young children can lead to premature closure of the skull sutures (craniosynostosis), further demonstrating the sensitivity of the developing skeleton to thyroid hormone levels [53, 54]. Additionally, maternal hyperthyroidism may also increase the risk of craniosynostosis in their children [55].

These observations emphasize the critical role thyroid hormones play in ensuring proper skeletal development throughout childhood.

4 Impact of TSH Variations on Bone Health

4.1 Bone Turnover Markers

While studies have explored the association between thyroid-stimulating hormone (TSH) levels and bone markers, the results have been inconsistent.

In postmenopausal women, higher TSH levels have been linked to increased bone turnover and stiffness. However, it's important to note that these studies did not assess free T3 and T4 levels, which could potentially influence bone metabolism [56].

Conversely, some studies have shown a negative correlation between TSH and bone resorption markers, such as urinary deoxypyridinoline [57]. However, these studies often included individuals with various thyroid conditions, making it difficult to isolate the specific effects of TSH on bone metabolism.

Further research is needed to clarify the complex relationship between TSH levels, bone markers, and bone health, particularly in premenopausal women and individuals with different thyroid conditions.

4.2 BMD

The relationship between thyroid function and bone mineral density (BMD) is complex and not fully understood. While some studies have shown an association between elevated TSH levels and increased BMD, others have reported a negative correlation, particularly with higher free T4 levels [58].

Several studies have suggested that higher TSH levels within the normal range may be associated with increased BMD, especially in postmenopausal women [59]. However, it's important to note that these studies often included individuals with various thyroid conditions, making it difficult to isolate the specific effects of TSH on bone health.

Conversely, studies have also shown that higher levels of free thyroid hormones, particularly free T4, may be associated with lower BMD. This suggests that a delicate balance between thyroid hormones is necessary for optimal bone health [60].

It's important to consider that these findings are often based on observational studies and may not necessarily reflect a causal relationship. Further research is needed to clarify the underlying mechanisms and to determine the clinical implications of these findings.

4.3 Fracturative Risk

The link between thyroid function and fracture risk is a complex one, and the research on this topic has produced mixed results. While some studies suggest that low TSH levels may increase the risk of fractures, especially in postmenopausal women, others have found no such correlation or even a protective effect of higher TSH levels [60].

Additionally, research has shown that elevated levels of free thyroid hormones (fT3 and fT4) within the normal range can be associated with a higher risk of fractures, particularly in postmenopausal women [61].

However, the exact mechanisms behind this relationship remain unclear. It's important to consider that factors such as age, sex, and underlying health conditions can influence the impact of thyroid function on fracture risk. Further research is needed to fully understand the complex interplay between thyroid hormones, bone metabolism, and fracture risk [62].

5 Impact of Hypothyroidism on Bone Health

Hypothyroidism can significantly impact bone metabolism. Histomorphometric studies have revealed a reduction in osteoblast activity, impaired osteoid mineralization, and decreased osteoclast activity, leading to a state of reduced bone turnover [63]. This results in a net increase in bone mineralization without a significant change in bone volume. However, the prolonged remodeling cycle associated with hypothyroidism can lead to an increase in bone mass over time [64, 65].

5.1 BMD

Consistent with histomorphometric findings, several studies have reported normal BMD in individuals with newly diagnosed hypothyroidism. However, the long-term effects of hypothyroidism, particularly on bone quality, remain less clear.

Cross-sectional studies have shown no significant differences in BMD between well-treated hypothyroid patients and healthy controls [66]. However, some longitudinal studies have suggested that hypothyroidism, even when treated, may be associated with reduced BMD, particularly in premenopausal women [67]. These findings are complex and may be influenced by factors such as the duration of hypothyroidism, the adequacy of treatment, and individual patient variability.

Further research is needed to fully understand the impact of hypothyroidism on bone health and to identify strategies for optimizing bone health in individuals with thyroid dysfunction.

5.2 Fracturative Risk

While the direct impact of thyroid hormone replacement therapy on fracture risk has not been definitively established, retrospective studies have not identified a clear association. However, large-scale population studies have revealed a link between a history of hypothyroidism and an increased risk of fractures, particularly in postmenopausal women [68, 69]. This increased risk may persist for several years after diagnosis and treatment.

Some studies have suggested that overtreatment with thyroid hormone, particularly in patients with additional hormonal deficiencies like growth hormone (GH) deficiency, may increase the risk of vertebral fractures [70]. Additionally, in postmenopausal women, high doses of thyroid hormone replacement therapy have been linked to an increased risk of fractures, particularly in those with a history of osteoporosis [71].

Overall, while hypothyroidism itself may not directly increase fracture risk, it's crucial to maintain optimal thyroid hormone levels to minimize the potential for bone health complications.

5.3 Consequences of Subclinical Hypothyroidism on Bone

Treatment of subclinical hypothyroidism with levothyroxine can lead to increased bone turnover, particularly in the short term [72]. However, long-term effects on bone mineral density (BMD) are less clear.

Several studies have investigated the association between subclinical hypothyroidism and BMD and fracture risk. While some studies have suggested a potential link, particularly in older men [73], others have found no significant association. A large meta-analysis of numerous studies has further reinforced the notion that subclinical hypothyroidism is not associated with an increased risk of fractures [74].

The complex relationship between subclinical hypothyroidism and bone health warrants further investigation. While short-term treatment with levothyroxine may influence bone turnover, the long-term benefits in terms of BMD and fracture risk remain uncertain.

6 Impact of Hyperthyroidism on Bone Health

6.1 BMD

Thyrotoxicosis accelerates bone turnover, increasing both bone formation and resorption. This heightened metabolic activity can lead to a net loss of bone mineral density, particularly in premenopausal women [75, 76]. Treatment of thyrotoxicosis can reverse this effect, leading to improvements in bone mineral density [77].

6.2 Fracturative Risk

While prompt diagnosis and treatment have reduced the risk of severe osteoporosis caused by uncontrolled hyperthyroidism, undiagnosed hyperthyroidism can still contribute to bone loss and osteoporosis in some patients who experience fractures [78]. Studies have also shown a potential link between hyperthyroidism and increased mortality rates in elderly patients with hip fractures [79].

The relationship between hyperthyroidism and fracture risk is complex. Several studies have found an association between a history of hyperthyroidism and fractures, but it's unclear whether this is due to reduced bone mineral density (BMD) caused by the thyroid disease, or if the hyperthyroidism itself contributes directly to fracture risk [80, 81].

6.3 Consequences of Subclinical Hyperthyroidism on Bone

Subclinical hyperthyroidism, characterized by a mild elevation of thyroid hormones without overt clinical symptoms, has garnered significant attention due to its potential impact on skeletal health. While the long-term consequences of TSH suppression remain a subject of ongoing research, the interplay between thyroid function and bone metabolism is intricate.

Numerous studies have investigated the relationship between TSH suppression in patients treated for thyroid cancer and bone turnover, as well as bone mineral density. The findings, however, have been inconsistent. While some studies suggest an increase in bone resorption and a subsequent decrease in BMD, particularly in postmenopausal women [82], others have not demonstrated a significant association [83].

The risk of fractures represents another critical aspect. Some epidemiological studies have shed light on the relationship between subclinical hyperthyroidism and fracture risk. There was found a significant association between endogenous subclinical hyperthyroidism and hip fracture risk in men, but not women [73]. However, other studies have yielded conflicting results, with some finding no association between subclinical hyperthyroidism and fracture risk, particularly in older men. While the exact mechanisms underlying this association remain unclear, it is believed that subclinical hyperthyroidism may contribute to bone loss and increased fracture risk through various mechanisms, including altered bone turnover, reduced bone m ineral density, and potential direct effects on bone cells.It is important to note that the impact of subclinical hyperthyroidism on bone health may vary depending on factors such as the severity of the condition, the duration of exposure to elevated thyroid hormone levels, and individual patient characteristics.

6.4 Thyroid hormone replacement therapy and skeletal outcomes

Systematic reviews have shown that long-term use of suppressive doses of thyroid hormone replacement therapy with levothyroxine (L-T4) in postmenopausal women can lead to a significant decrease in bone mineral density (BMD). This reduction, estimated to be around 7% at the lumbar spine and 5% at the hip over 8.5 years, highlights the importance of monitoring bone health in this population [84, 85].

7 Conclusions

The intricate relationship between thyroid hormones and bone health is a multifaceted one, impacting both bone development and adult bone maintenance. Thyroid hormone deficiency, particularly in children, can lead to impaired growth and bone maturation.

Conversely, excessive thyroid hormone levels, as seen in hyperthyroidism, can accelerate bone turnover and lead to bone loss, especially in postmenopausal women.

The thyroid-stimulating hormone (TSH) also plays a role in bone metabolism, although its exact mechanisms of action are not fully understood. While some studies suggest that TSH can influence bone turnover, further research is needed to clarify its precise role.

In clinical practice, a careful assessment of thyroid function is essential for individuals with bone disorders. Optimal thyroid hormone levels are crucial for maintaining bone health, and appropriate treatment can help prevent or mitigate bone loss.

Future research should continue to investigate the complex interplay between thyroid hormones, bone cells, and the factors that influence bone health. By gaining a deeper understanding of these mechanisms, we may develop novel therapeutic strategies to prevent and treat bone diseases associated with thyroid dysfunction.

Questions for Self-Assessment

1. *Which of the following statements about TSH and bone health is correct?*

   (a) TSH has no influence on bone metabolism.
   (b) High TSH levels are always associated with increased bone resorption.
   (c) TSH may influence bone turnover, but evidence is conflicting.
   (d) TSH directly inhibits osteoblast differentiation.

   Correct answer: (c) TSH may influence bone turnover, but evidence is conflicting
2. *What is the typical effect of untreated hyperthyroidism on bone health?*

   (a) Decreased bone turnover and increased BMD
   (b) Increased bone turnover and decreased BMD
   (c) Normal bone turnover and unchanged BMD
   (d) Reduced risk of fractures

   Correct answer: (b) Increased bone turnover and decreased BMD
3. *In postmenopausal women, which thyroid-related condition is most associated with increased fracture risk?*

   (a) Well-controlled hypothyroidism
   (b) Subclinical hypothyroidism
   (c) Elevated TSH levels
   (d) Subclinical hyperthyroidism

   Correct answer: (d) Subclinical hyperthyroidism

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Formulations for the Replacement Therapy of Hypothyroidism: State of the Art and Perspectives

Marina Lugaresi and Laura Fugazzola

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Chapter Introduction: What You Will Learn in This Chapter
Levothyroxine (LT4) has been the standard therapy for hypothyroidism since the 1970s. To date, LT4 is available as tables, soft gel capsules, and liquid formulations. Liquid and soft gel formulations can be considered in patients with clinical conditions that reduce gastric acidity or with intestinal diseases associated to malabsorption. These formulations may also be useful in children due to their easier way of administration, and in pregnant women with hyperemesis.

Beside LT4 monotherapy, triiodothyronine-thyroxine combination therapy can be considered in selected hypothyroid patients complaining symptoms despite biochemical tests indicating adequate replacement, mainly after thyroid surgery.

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Learning Objectives
At the end of this chapter, you will be familiar with the different formulations available for the treatment of hypothyroidism.

Definitions
- *Levothyroxine* is a synthetic hormone that is biochemically and physiologically identical to endogenous thyroxine and is used to replace reduced thyroid function.
- *Tablet levothyroxine* is a formulation containing the sodium salt of levothyroxine with various excipients.
- *Soft gel levothyroxine* is a capsule formulation consisting of levothyroxine dissolved in glycerine and surrounded by a layer of gelatine.
- *Liquid levothyroxine* is an oral solution made from glycerine or ethanol in which levothyroxine is dissolved.

1 Introduction

Hypothyroidism is the condition of reduced thyroid function due to either primary or central disease. Primary hypothyroidism has a high prevalence globally, with overt forms affecting approximately 3% of the general population and an estimated annual incidence of 226 per 100,000 individuals [1, 2]. The leading causes of hypothyroidism are autoimmune thyroiditis and thyroidectomy [1]. Independently from the underlying cause, reduced or absent thyroid function must be corrected, trying to avoid either an undertreatment or an overtreatment. Initially, animal thyroid extracts were employed for thyroid function replacement in humans, and were abandoned since 1970, with the advent of synthetic LT4. Currently, the bioidentical synthetic thyroxine (levothyroxine, LT4) is the standard of care of hypothyroidism management [3], replacing the function of endogenous-produced thyroxine. Given that approximately 80% of the bioactive thyroid hormone, namely, triiodothyronine (T3), derives from peripherical conversion of thyroxine (T4) [4], LT4 offers a safe and efficient therapeutic approach, and allows to reestablish biochemical and clinical euthyroidism.

In addition to replacement therapy, during the thyroid cancer follow-up, LT4 treatment can be used for suppressive or semi-suppressive therapy, with a thyroid-stimulating hormone (TSH) target lower than 0.1 mU/L or between 0.1 and 0.5 mU/L, respectively.

2 L-Thyroxine Formulations

LT4 tablets have been the only preparation available for several years, while more recently different formulations have been made available for commercial use, including liquid oral solutions, and soft-gel capsules (Table 1). While tablets contain LT4 sodium-salt mixed with various excipients, the other formulations are

Table 1 Different L-thyroxine (LT4) formulations available to date

LT4 formulation	Use	Disadvantage
Tablet	Most used Patient personal preference	At least 30' between intake and breakfast Acid pH required Needs to be swallowed
Soft gel capsule	Reduced gastric acidity Patient personal preference	Costly
Liquid oral solution	Reduced gastric acidity Infants Unable to swallow Enterally fed Patient personal preference	Difficulties in emptying mono-dose vials Bulky packaging
Intravenous	Myxedema coma	Hospital administration Costly

based on pre-dissolved levothyroxine. Specifically, soft-gel capsules contain LT4 dissolved in glycerin and encased in a gelatin layer that readily dissolves in the stomach. Conversely, LT4 in liquid solutions is dissolved in glycerol or ethanol [5]. Oral bioavailability typically ranges between 70% and 80%, but it depends on the formulation, the dissolution, and the transporter-dependent intestinal absorption, the peak concentration reaching in 1.5–3 h [6, 7]. While these formulations are bioequivalent, significant differences have been shown in the time taken to reach peak blood concentration, notably between liquid LT4 and others [8], and between soft gel and tablet formulation [9]. Moreover, ethanol-dissolved liquid formulations are stable in hot milk, coffee, and tea (50 °C) and in room temperature juice [10].

The main difference among formulations lies the pre-absorption phase, because LT4 salt needs to be dissolved. The gastric environment plays a pivotal role, as low pH is required for the conversion from salt to its native form, enabling subsequent intestinal absorption. Consequently, to optimize absorption, tablets should ideally be taken 30–60 min before breakfast or 3 h after dinner to ensure fasting conditions and an acidic environment [3]. On the contrary, liquid and soft-gel formulations are stable regardless the pH [11]. Although the differences are not significantly different, soft-gel formulations seem to lead to an increased bioavailability and to a higher absorption peak within the first 60–180 min compared to tablets, potentially leading to an enhanced efficacy in lowering TSH levels [12]. Following absorption, orally administered LT4 undergoes the same metabolic processes as endogenous T4, irrespective of the formulation type.

Considering that Proton Pump Inhibitors (PPI) increase gastric pH, patients treated with both PPI and LT4 may benefit from ethanol-dissolved LT4 formulation [13] or soft-gel capsule [14].

Once dissolved, LT4 absorption depends on intestinal wall integrity, with the jejunum and ileum being the most involved tracts. Additionally, various elements such as coffee, food, and other medications (e.g., sucralfate, aluminum, calcium carbonate/acetate/citrate, iron, cholestyramine, rifampicin, carbamazepine, phenytoin) can delay LT4 absorption. In particular, it is advisable to avoid fiber and soy-based products during breakfast, take tablets with water rather than coffee, and administer calcium and iron supplements 4 h apart from LT4 intake, when feasible [3].

Based on some study, pre-dissolved LT4 formulations may be beneficial for patients with low adherence to therapy due to coffee consumption close to T4 ingestion [15], those requiring concomitant treatment with calcium or iron [12], or those who have undergone bariatric surgery [16]. Similarly, soft-gel or liquid formulations may be useful in patients with gastrointestinal diseases leading to LT4 malabsorption, such as celiac disease, atrophic gastritis, lactose intolerance, diabetic gastroparesis, giardiasis, and *Helicobacter pylori* infection [12, 17]. However, studies comparing tablets and liquid/soft-gel formulations in the presence of comorbidities or concomitant drug intake are often small, unblinded, and retrospective or case-reports, thus no strict indications can be inferred [12].

After oral administration of LT4 tablets, 60–90% of the drug is absorbed within 3 h. Hence, patients receiving enteral nutrition should cease feeding 30 min to 2 h before and after LT4 intake [18]. On the contrary, liquid LT4 is predicted to be absorbed without interrupting enteral feeding, thus simplifying the management [18]. In this context, the syringe method of delivery is usually preferred.

Apart from dissolution issues, liquid formulations offer other advantages such as ease of swallowing (particularly beneficial for children and the elderly), improved compliance due to the short interval between drug intake and breakfast/coffee consumption, and reduced interference with other medications.

Given that a considerable portion of patients (20%) consume food within 30 min of LT4 ingestion [19], the switch to liquid oral solution may enhance adherence in those unwilling to change their routines [20]. Nevertheless, if the LT4 administration in tables is warranted by the clinician or requested by the patient, an increase in the dosage is usually able to overcome reduced absorption related to gastrointestinal comorbidities [21, 22].

On the other hand, one of the primary drawbacks of liquid formulations is the taste, reported as distasteful by 11% of patients [20]. Additionally, some patients do not like liquid formulations either due to the bulkier packaging or to the difficulties in the complete emptying of single-dose plastic vials or to the longer time for the preparation of the exact dose with the syringe method with respect to tablets. In this context, vials probably offer a less precise and constant dosage with respect to tablets, soft gel capsule, and syringe.

Guidelines recommendations emphasize the opportunity to maintain during the chronic treatment the same brand and formulation to avoid potential fluctuations in thyroid hormones and TSH levels. Therefore, changes in the formulation should be considered only when clinically warranted or requested by the patient.

3 LT4 Treatment in Pregnancy

Alterations in thyroid function in pregnant women can have important repercussions for both the mother and the fetus (increased prevalence of miscarriage, preterm birth, postpartum hemorrhage, low birth weight, and neuropsychological alterations). Dosage increases are needed in 50–85% of pregnancies, with an

increase of 25–50% compared to preconceptional values and return to basal dosages in the majority of women after childbirth. This increase is due to the following issues: (a) need to supply thyroid hormone to the fetus, (b) increased TBG levels as a result of increased estrogenic concentration that leads to a reduced hepatic clearance of this protein; (c) reduced absorption of thyroxine, for example, for iron and calcium intake and for hyperemesis gravidarum. Due to hyperemesis and the concomitant medications, liquid solutions are usually preferred by pregnant women.

4 LT4 Treatment in the Pediatric Population

Congenital hypothyroidism affects approximately 1 in every 2000–3000 newborns annually. Initiation of treatment within the first 14 days of life is crucial to prevent adverse neurodevelopmental outcomes [23]. Liquid formulations may be more suitable for children and newborns compared to crushed tablets (an off-label procedure). Both should be diluted in water or breastmilk before administration [23]. Even if a glycerol solution may be preferred, the alcohol content in ethanol-dissolved LT4 does not exceed the daily threshold for children set by the American Academy of Pediatrics [5, 24, 25]. When switching from tablets to liquid formulation, careful dose adjustments are necessary to prevent overtreatment, given the potentially higher bioavailability of the latter [23]. It should be considered that frequent dosage changes are necessary in children and adolescents as a consequence of growth and changes in metabolism. On the other hand, it is of fundamental importance that the replacement dose is adequate in this particular phase due to the possible negative effects on skeletal and neurological development and therefore on school and sports performance of both excessive and insufficient dosage. TSH assessment is generally performed 4–8 weeks after each dosage change.

5 Unusual Formulations

There are unconventional ways to administer LT4, including intravenous, intramuscular, and rectal routes.

Intravenous LT4 is only approved for the treatment of myxedema coma. However, this formulation can be also used in patients unable to orally assume LT4, particularly during emergencies or enteral nutrition, as more than 50% of enterally fed patients experience inadequate LT4 absorption [1, 26, 27].

There are some case reports describing the use of intravenous LT4 to treat resistant forms of hypothyroidism, often with a weekly administration [28, 29]. It is worth noting that the cost of intravenous solutions is significantly higher compared to tablets [26].

Administration of LT4 via intramuscular, subcutaneous, rectal, and sublingual routes is described anecdotally [1, 26, 30]. Intramuscular injection may serve as an

alternative route for patients with myxedema coma or those unable to swallow, offering a sustained-release drug delivery administrable once or twice a week [1]. Similarly, according to some case reports, subcutaneous injections provide a long-release administration, resulting in fewer fluctuations in TSH levels and slower release compared to intramuscular injections, with the added benefit of potential patient self-administration once or twice a week [1].

Rectal administration offers an alternative route for patients unable to take oral formulations, with short bowel syndrome or gastrointestinal tract obstruction. Since LT4 suppositories are not widely available, intravenous LT4 preparations or extemporaneous tablet-dissolved solutions may be used. However, it is worth noting that, although rectal administration bypasses the hepatic first-pass effect, it may necessitate doubling the LT4 dose to normalize plasma TSH levels, possibly due to differences in intraluminal pH [1].

In the future, the development of subcutaneous devices for LT4 delivery or long-acting formulations may provide additional options for administration [1].

6 LT3-LT4 Combination Therapy

While most patients achieve euthyroidism with LT4 treatment, some complain an inability to attain pre-disease levels of well-being, despite biochemical tests indicating adequate replacement. Some studies described different LT4/LT3 ratio in patients treated with LT4 compared to euthyroid individuals, but none of the numerous randomized clinical trials and metanalysis found a significant benefit in administering LT3 in combination with LT4 [31]. Currently, the optimal approach to thyroid hormone replacement therapy remains a subject of debate among experts. Both the European Thyroid Association (ETA) and the American Thyroid Association (ATA) state that there is insufficient evidence to recommend combination therapy over LT4 alone. Nevertheless, they suggest considering a trial of combined T3-T4 therapy in selected patients who do not respond adequately to LT4 monotherapy [3, 32]. LT3 should be considered in patients who specifically request it, exhibit persistent marked symptoms, and fully understand and accept (with written/documented information if possible) the unknown potential long-term risks [31]. If the combination therapy trial fails after 3 months, it should be discontinued, and LT4 monotherapy reintroduced [32].

T3 is available in tablets and liquid solutions. Even if combined T3–T4 tablets are available, they typically contain an excessive amount of T3, therefore the association of two separate medication is recommended [32]. Currently, there are no commercially available slow-release T3 formulations.

7 Desiccated Thyroid Extract

Desiccated thyroid extract (DTE) is the cleaned, dried, and powdered thyroid gland, deprived of connective tissue and fat, and obtained from animals that are used for human food consumption [31]. Most formulations are derived from porcine or bovine thyroids or a combination of both [31]. DTE is often prescribed in grains, with each grain typically containing around 60–65 mg of DTE, comprising approximately 38 μg of T4 and 9 μg of T3. Consequently, DTE grains contain a supraphysiological dose of T3, which contributes to the reduced safety of these products and complicates their management. Additionally, there is an important variability in thyroid hormone content among different batches, adding further challenges to therapy management. Both ETA and ATA guidelines strongly discourage the use of DTE [3, 32].

8 Drawbacks and Perspectives

More studies are definitely needed to fully address pros and cons of the different LT4 formulations. Indeed, many drawbacks exist in the data available to date, such as the paucity of randomized and controlled studies, and the non-standardized meal in food interference studies. Moreover, the residual thyroid function in patients with autoimmune hypothyroidism is usually not considered, and the pediatric and elderly populations are underrepresented in most studies.

Finally, future studies will clarify if liquid formulations can actually be taken during meals, the degree of patient's satisfaction with the different formulations, the time to reach the final dose, the difference in the frequency of dose adjustments, and the global cost-effectiveness.

Take-Home Messages

Tablets are to date the most used LT4 formulation, although the use of soft-gel capsules or liquid oral solutions may be planned in specific settings, considering that a wide consensus is still lacking. Several open questions remain unanswered, such as the existence of absorption sites other than the small intestine, the reasons why food and drugs do not interfere with the absorption of pre-dissolved LT4, and the optimal timing and formulation for patients receiving enteral nutrition. Beyond oral and intravenous administration, other routes have been anecdotally described in literature. Lastly, for selected patients experiencing symptoms despite adequate LT4 monotherapy, a trial of combined LT3 and LT4 may be considered, avoiding the use of desiccated thyroid extracts.

Questions for Self-Assessment

1. *Which of the following is the primary objective of thyroid hormone replacement therapy in patients with hypothyroidism?*

   (a) To increase the metabolic rate
   (b) To restore normal thyroid hormone levels in the blood
   (c) To promote weight loss
   (d) To reduce the size of the thyroid gland

   Correct answer: (b) To restore normal thyroid hormone levels in the blood
2. *Which of the following thyroid hormone formulations is most commonly used in the treatment of hypothyroidism?*

   (a) Levothyroxine sodium
   (b) Liothyronine sodium
   (c) Desiccated thyroid extract
   (d) Triiodothyronine (T3)

   Correct answer: (a) Levothyroxine sodium
3. *What is a potential limitation of levothyroxine therapy in hypothyroidism?*

   (a) It can cause hyperthyroidism in some patients
   (b) It requires the patient to take it with food for better absorption
   (c) It does not adequately convert to T3 in some individuals
   (d) It is only available in injectable form

   Correct answer: (c) It does not adequately convert to T3 in some individuals

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Pharmacological Interactions of Levothyroxine in Multiple-Treated Patients

Francesco Di Marco and Claudio Cusini

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Chapter Introduction: What You Will Learn in This Chapter
This chapter explores the pharmacological interactions of levothyroxine (LT4) in patients who are on multiple medications. As hypothyroidism often coexists with other chronic conditions, understanding how various drugs influence LT4's absorption, distribution, metabolism, and action is essential for optimal patient care.

The chapter delves into common interfering drugs, mechanisms of interaction, and clinical implications such as altered thyroid function test results and symptoms of hypo- or hyperthyroidism. It offers practical recommendations for dosing, timing, and monitoring strategies to help clinicians manage LT4 treatment effectively in complex therapeutic settings.

Key Points
- Pharmacokinetic profile of LT4 and how it is altered by other drugs
- Absorption-altering agents (e.g., calcium, iron, PPIs, bile acid sequestrants)
- Metabolism-enhancing drugs (e.g., anticonvulsants, rifampin)

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- Monitoring and dose-adjustment strategies in polypharmacy
- Recognizing and preventing therapeutic failures or iatrogenic thyrotoxicosis

Learning Objectives
By the end of this chapter, readers will be able to:

- Explain the pharmacokinetics of levothyroxine and how other drugs can modify it
- Identify common drugs that interfere with LT4 therapy
- Understand the clinical relevance of LT4 interactions in polymedicated patients
- Implement evidence-based strategies to optimize LT4 efficacy and patient outcomes

Definitions
- *Levothyroxine (LT4)*: A synthetic form of the thyroid hormone T4, used to treat hypothyroidism.
- *Pharmacological interaction*: The alteration of a drug's effect due to the presence of another drug.
- *Bioavailability:* The proportion of a drug that reaches systemic circulation in its active form.
- *Enzyme induction*: The process by which certain drugs increase the activity of liver enzymes, leading to faster drug metabolism.
- *Polypharmacy*: The concurrent use of multiple medications, often increasing the risk of drug–drug interactions.

1 Treatment of Hypothyroidism

Levothyroxine (L-T4) has long been considered the standard therapy for treating hypothyroidism. With this therapy, most patients experience remission of their hypothyroidism symptoms and signs, and its prolonged serum half-life allows for daily administration. However, a small percentage of hypothyroid patients report that L-T4 fails to relieve their symptoms [1]. Recently, endocrinologists have emphasized the need for an individually tailored dose; indeed, many patients do not show a clinical and/or biochemical response, requiring larger doses of thyroxine to achieve the desired blood TSH values [2], along with increased health costs for repeated diagnostic procedures [3].

Hypothyroidism symptoms are nonspecific, including, but not limited to, weight gain, puffiness, dry skin, cold intolerance, constipation, slowed heart rate, muscle cramps, voice changes, delayed relaxation of ankle reflexes, and coarse skin. These symptoms often have an insidious onset and overlap significantly between patients with thyroid disease and those without, showing relatively high specificity but very low sensitivity [1].

Carpal tunnel syndrome, sleep apnea, pituitary hyperplasia (which can occur with or without hyperprolactinemia and galactorrhea), and hyponatremia are less common but still recognized conditions typically associated with severe hypothyroidism [4].

The guidelines for the treatment of hypothyroidism, prepared by the American Thyroid Association Task Force on thyroid hormone replacement, identify three primary objectives of levothyroxine replacement therapy (with moderate-quality evidence and strong recommendations), which are as follows: (1) to alleviate symptoms and signs of hypothyroidism, including the restoration of biological and physiological markers; (2) to restore serum thyrotropin levels along with improvements in thyroid hormone concentrations; and (3) to prevent overtreatment (iatrogenic thyrotoxicosis), particularly in the elderly [1].

In general, the evaluation of the effectiveness of replacement therapy from a purely clinical perspective is made more challenging by the lack of specificity of hypothyroid symptoms and signs. In the case of autoimmune thyroid disease (AITD), the gradual development of the pathological state further complicates this evaluation. The guidelines suggest that signs and symptoms should be monitored but considered in the context of serum thyrotropin values, relevant comorbidities, and other potential causes [1]. Moreover, undertreatment and overtreatment with L-T4 should be avoided due to documented detrimental effects.

Even though L-T4 is widely considered the standard treatment for hypothyroid patients, based on its documented efficacy, long-term experience, favorable biochemical profile, and low cost, other thyroid hormone preparations are also commercially available. These alternative treatments include thyroid extract preparations, L-T3 preparations, and preparations containing a mixture of L-T4 and L-T3 [5].

While the clinical use of desiccated thyroid extract and L-T3 preparations is not advisable due to their adverse events, such as the high risk of developing atrial arrhythmias or, for L-T3 preparations, the progression of acute myocardial ischemia [6, 7], combination therapy with both L-T4 and L-T3 is considered by some clinicians, particularly in patients who have undergone total thyroidectomy. The rationale for combined therapy after total thyroidectomy comes from recent data showing that athyreotic individuals may have low T3 levels, resulting in a higher-than-normal FT4-to-FT3 ratio [8]. Moreover, during treatment with L-T4 alone after total thyroidectomy, higher FT4, lower FT3 levels, and a lower FT3/FT4 ratio were found compared to those after partial thyroidectomy, suggesting that T3 production by the remnant thyroid tissue is important to maintain normal postoperative serum T3 levels [9]. This could explain a possible clinically relevant role in the persistence of hypothyroid or nonspecific symptoms during L-T4 therapy alone [10, 11].

Despite these studies, there is still no consensus or convincing evidence that combined therapy is more beneficial than treatment with L-T4 alone. In fact, both the ETA (European Thyroid Association) and ATA (American Thyroid Association) guidelines strongly recommend that L-T4 monotherapy remains the therapy of choice in hypothyroidism due to insufficient evidence of the superiority of combination treatment and because it is considered the safest therapy currently [1, 4, 12]. We must also consider the potential adverse events of combined therapy on bone and heart health, especially on heart rate and the possibility of arrhythmias.

2 Pharmacokinetics and Characteristics of Levothyroxine

Levothyroxine is the levo-isomer of thyroxine. Its most common pharmaceutical form is the pentahydrated sodium salt of T4 [13]. This form is used in all oral thyroxine preparations, which are considered the safest and most preferred by patients [14].

Oral levothyroxine is absorbed by the jejunoileal tract, with a small portion absorbed by the duodenal mucosa at the intestinal level. Absorption in the stomach is excluded by studies showing the lag time between thyroxine ingestion and its appearance in plasma [15]; similarly, no absorption has been described in the large bowel. The stomach appears to have an impact on oral thyroxine bioavailability due to its physiological pH variations, which, in some situations, could lead to an increased need for the drug: this is the so-called gastric-phase, a prerequisite for intestinal drug absorption [16]. In contrast, some studies suggest the possibility of passive diffusion through the gastric wall, as happens with other small compounds. Once the drug reaches the stomach, it first undergoes disintegration. This process causes the release of the active ingredient from the solid form, and it is affected by the type of formulation and the excipients used. The fasting or fed state, gastric residence time, and gastric motor function affect the disintegration process [17]. It then undergoes dissolution, which consists of the release of solute molecules from the solid phase into the liquid phase, represented by the gastric juice. A prerequisite for successful absorption is that the active ingredient is in aqueous solution. Changes in stomach pH might affect its dissolution, along with its oral availability and, consequently, its absorption, with the highest absorption rates occurring at lower pH values. The process of dissolution can also be affected by particular physicochemical conditions, including gastric juice viscosity, the type of excipients, and the size and shape of the active ingredient particles [18, 19].

Finally, it reaches the small intestine. Absorption by the duodenal mucosa is regulated by its integrity, motility, mucous composition, and resident microbial population. Absorption in the small intestine is incomplete, with approximately 70% of the administered dose being absorbed. The percentage of absorption along the whole small intestine (mean values) is 15% ± 5% in the duodenum, 29% ± 14% in the upper jejunoileum, and 24% ± 11% in the lower jejunoileum [20]. Here, it undergoes transport across the mucosa through different mechanisms. Passive diffusion is considered a secondary transport route [21], while the main pathway involves specific carriers that facilitate the passage of levothyroxine through the intestinal mucosal cells. The main transporters are the monocarboxylate transporter family (MCT), the organic anion-transporting polypeptide (OATP) family, the ATP-binding cassette transporter superfamily, and the large neutral amino acid transporter family [22]. After intestinal transport, T4 reaches the target organs where its peripheral metabolism takes place. It is affected by different metabolic pathways: deiodination, hepatic conjugation with sulfuric and glucuronic acids (which allow for renal and biliary clearance), and binding to the intestinal microbial flora, which creates a hormonal reservoir [23]. Moreover, intestinal microbiota also contributes

to the deconjugation of thyroid hormones, with their possible hepatic reuptake through portal circulation. Thus, alterations in microbiota may affect thyroid hormone metabolism [20].

3 Interference with Thyroxine Effectiveness

Several mechanisms affect the absorption of levothyroxine at different levels of the gastrointestinal tract. The following mechanisms outlined below appear to impact every stage of oral thyroxine absorption and metabolism, primarily by:

1 Altering the pH of the stomach, thereby impairing the process of disintegration and dissolution.
2 Competing with intestinal transporters at the intestinal level.
3 Influencing the binding of thyroxine to plasma proteins.
4 Modifying the mechanisms involved in the catabolism of thyroxine [16].

In the following explanation, when referring to L-T4, unless specified otherwise, we specifically mean the tablet formulation. For detailed information about other formulations (e.g., liquid form, softgel), see chapter "Formulations for the Replacement Therapy of Hypothyroidism: State of the Art and Perspectives".

4 Levothyroxine Interactions with Food and Drinks

Firstly, food can alter thyroxine effectiveness, especially through the first two mechanisms mentioned, which are associated with an increased need for thyroxine. Moreover, food may act as a barrier to the bioavailability of thyroxine itself. See Table 1.

Table 1 Food and drinks which can alter L-T4 tablet absorption

Food and drinks	Mechanism of interaction	Recommendations
Milk	Gastric absorption (calcium)—reduction of intestinal absorption by milk proteins	Posticipate assumption by at least 1 h from L-T4
Coffee	Reduction of intestinal absorption	Posticipate assumption by at least 1 h from L-T4
Fibers	Reduction of intestinal absorption	Posticipate assumption by 3–4 h from L-T4
Soy	Reduction of intestinal absorption	Posticipate assumption by 3–4 h from L-T4
Papaya	Gastric juice alkalinization	Posticipate assumption, evitate large ingestions
Grapefruit juice	Inhibition of intestinal transporters	Limited data

4.1 Papaya

Deiana et al. reported a case of an unexpected increase in TSH levels in a 37-year-old thyroidectomized patient on L-T4 therapy, who had consumed large amounts of papaya during his vacation. They hypothesized that the active compound in the fruit (papain) reduces gastric acid secretion for up to 48 h (by reducing the histamine-induced acid secretion), and this gastric alkalinization is associated with reduced L-T4 absorption. Moreover, papaya also contains fiber, which may interfere with L-T4 absorption at the intestinal level when consumed in large amounts [24]. It is recommended to postpone its consumption and avoid excessive intake of the fruit.

4.2 Milk

Chon et al. conducted a pharmacokinetic study in healthy euthyroid subjects to assess levothyroxine absorption with and without concurrent cow's milk consumption. They found that consuming cow's milk concurrently with levothyroxine reduces oral absorption, probably due to the milk's protein content, alkaline pH, and calcium levels—all of which interfere with levothyroxine absorption [25]. It is suggested to delay milk consumption by at least 1 h after L-T4 intake.

4.3 Fiber, Soy, and Coffee

Soy, fiber, and coffee can bind oral thyroxine at the intestinal level. Several reports suggest that feeding soy-based formulas to infants with congenital hypothyroidism may lead to malabsorption of L-T4 tablets and increased TSH levels. In particular, it seems that soy protein and soy isoflavones are responsible for this decreased absorption [25, 26]. These compounds disrupt the entero-hepatic circulation, which levothyroxine undergoes, thereby directly reducing intestinal L-T4 absorption. For this reason, it is advisable to postpone soy consumption for at least 4 h.

A fiber-enriched diet or fiber supplements significantly affect the bioavailability of L-T4. Increased bowel movements can delay L-T4 absorption [27]. Considering the physiological entero-hepatic cycle of T4, even if T4 is taken separately or parenterally, dietary fiber may still interact with the hormone during its recycling through the intestine. As a result, T4 clearance may increase, while absorption is reduced, regardless of the timing of fiber ingestion. Therefore, stricter monitoring of TSH concentrations is advised for patients on L-T4 therapy who change their diets to include a high fiber intake [28]. In these cases, it is recommended to delay fiber consumption by at least 4 h.

Coffee does not change gastric pH, gastric emptying time, or intestinal transit. However, it interacts with L-T4 absorption by reducing the hormone's availability at

the intestinal level [29]. Different studies suggest that euthyroidism can be restored by postponing coffee consumption by at least 30 min to 1 h after taking L-T4 [30–32].

4.4 Grapefruit Juice

Grapefruit juice interferes with L-T4 absorption by blocking the specific transporters that help carry the hormone from the small intestine to the bloodstream. These transporters include the monocarboxylate transporter family (MCT), the organic anion-transporting polypeptide (OATP) family, and the sodium-taurocholate cotransporting polypeptide (NTCP). By inhibiting these transporters, grapefruit juice slightly delays the absorption of levothyroxine, but it seems to have only a minor effect on its bioavailability [33]. Literature reports limited and contradictory data from different case reports, so L-T4-treated patients should not be discouraged from consuming fruit juice in moderation [25].

5 Levothyroxine Interactions with Drugs and Supplements

Since L-T4 tablets are among the most prescribed medications, co-administration with interfering drugs is a common occurrence, potentially leading to undertreatment in up to 20% of patients with primary hypothyroidism.

5.1 PPI (Proton Pump Inhibitors): Cimetidine

The primary effect of PPIs is the increase in gastric juice pH, which is thought to be the most significant factor in altering the disintegration and dissolution phases of thyroxine tablets. However, PPIs also have a more complex impact on the pharmacokinetics of levothyroxine, potentially due to long-term use. This may lead to alterations in gastrointestinal physiology, such as changes in intestinal microbiota and the viscosity and composition of gastric mucus [34]. Cimetidine has a similar effect by alkalinization of pH of gastric juice. It is generally recommended to delay the administration of these medications by at least 3–4 h after taking L-T4.

5.2 Antacids

Several case reports and in vitro studies have indicated that aluminum hydroxide affects T4 absorption by influencing both gastric and intestinal processes [35]. A study by Liel et al. [36] on five hypothyroid patients receiving L-T4 therapy

showed an increase in serum TSH levels after introducing aluminum hydroxide tablets four times a day. Additionally, sucralfate has been reported to reduce maximum T4 absorption by 70%, significantly delaying the absorption process [37] by binding to L-T4 in a gastric acid environment. However, other studies did not confirm these findings. Clinical practice generally recommends delaying the use of antacids by at least 2–4 h for aluminum hydroxide and up to 6 h for sucralfate after L-T4 intake.

5.3 Orlistat

It inhibits gastrointestinal lipases being minimally absorbed. There are two case reports of interaction between orlistat and L-T4, likely due to the malabsorption of L-T4. It is advised to separate the administration of orlistat and L-T4 by at least 4 h and to increase the monitoring of thyroid hormone levels [38].

5.4 Cholestyramine Resin

Cholestyramine is an ion-exchange resin used to lower serum cholesterol. It interferes with thyroid hormone absorption and, similar to soy and fiber, inhibits the enterohepatic recycling of hormones, thus reducing circulating serum L-T4.

5.5 Vitamin C

Vitamin C (ascorbic acid) can enhance the absorption of L-T4, leading to lower TSH levels. Conversely, increasing gastric pH has been shown to reduce L-T4 absorption [39]. In clinical practice, it is advised not to take this supplement simultaneously with L-T4.

5.6 Calcium

Different calcium salts (acetate, citrate, and carbonate), particularly calcium carbonate, can reduce the bioavailability of T4. In vitro, calcium carbonate binds to thyroxine in a dose-dependent manner at a gastric pH of 2, and this binding disappears when the pH rises to 7.4. This process prevents intestinal absorption of L-T4, explaining its reduced absorption and altered pharmacokinetics—this characteristic also applies to other calcium salts [34]. Irving et al. demonstrated in a study on 450 patients on L-T4 with co-administered calcium preparations that the calcium

supplements can decrease L-T4 absorption [10]. It is suggested to separate the administration of calcium and L-T4 by at least 4 h.

5.7 Iron

The impaired absorption of L-T4 when taken with iron salts occurs due to the formation of soluble complexes with ferrous salts. Studies by Campbell et al., Shakir et al., and several case reports [40–42] have shown the onset of hypothyroidism in L-T4 treated patients, after the introduction of ferrous salt preparations. It is recommended to maintain a 4–6 h interval between the administration of these drugs. A study by Atruktsang et al. [43] on 605 patients treated with L-T4 found that iron supplementation could require prolonged L-T4 dose adjustments.

5.8 Bisphosphonates

Alendronate, a commonly used bisphosphonate for osteoporosis treatment, is typically administered once a week. It should be taken at least 30 min before breakfast or any other medications, as other drugs may reduce its absorption. Potential interactions between alendronate and L-T4 could involve a physicochemical interaction between the products in the intestinal lumen. H.G. Bone et al. conducted a three-way crossover study in 30 healthy adults, where subjects were dosed three times, separated by 35 days, after overnight fasts, with alendronate (70 mg), L-T4 alone, or both drugs concurrently. The results indicated that co-administration of alendronate with L-T4 does not affect the pharmacokinetics of L-T4, as no significant differences in serum L-T4 concentrations were observed after taking the drugs together [44].

5.9 Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) may cause de novo hyperthyroidism or hypothyroidism. Patients with athyreosis who were administered imatinib, motesanib, sorafenib, sunitinib, and vandetanib saw a necessity of increasing L-T4 requirements [45]. A possible mechanism for this increase is the inhibition of MCT8-dependent T3 and T4 uptake, as MCT8 is expressed in the gastrointestinal tract [46].

5.10 Enteral Nutrition

Enteral nutrition is used in various diseases and clinical conditions to assist malnourished or inadequately fed patients, aiming to improve prognosis and clinical outcomes. Pirola et al. conducted a study with 20 euthyroid patients 1 day after

surgery, evaluating the effect of different L-T4 formulations. They stopped enteral nutrition for 30 min before and after administering crushed L-T4 tablets and placing the liquid form concomitant to the continuous enteral nutrition. They measured thyroid hormone levels before and after L-T4 treatment with both formulations and found comparable results. Altered L-T4 absorption can occur when the tablet formulation is ingested with food, so it is recommended to switch L-T4 therapy from tablets to liquid formulations [47].

5.11 Oral Semaglutide

Oral semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) that stimulates the GLP-1 receptor, leading to reduced food intake, increased energy expenditure, and improved glycemic control. Hauge et al., in an open-label, one-sequence crossover trial with 45 healthy subjects, who received single-daily dose of L-T4 with oral semaglutide 14 mg, found that the pharmacokinetics of thyroxine were influenced by the co-administration of semaglutide. They demonstrated that the delay in gastric emptying caused by GLP-1RAs resulted in a longer transit time for co-administered oral drugs in the gastrointestinal tract, thereby providing a longer time-window for absorption. Therefore, they recommend close monitoring of thyroid function after starting the drug. Alternatively, it is suggested to switch to a liquid formulation or adjust the timing of semaglutide administration while maintaining a fasting state [48].

6 Other Drugs Involved in Altering Thyroid "Homeostasis"

Patients receiving thyroid hormone replacement therapy are also susceptible to drug interactions that affect thyroid "homeostasis," at multiple levels, e.g., acting at different levels of hypothalamus-pituitary-thyroid axis or on the thyroid hormone metabolism. These interactions can necessitate an increase or decrease in L-T4 dosage to achieve euthyroidism. Drugs can influence thyroid "homeostasis" in various ways: affecting the hypothalamic-pituitary control of the thyroid, affecting the thyroid hormone synthesis or release, enhancing thyroid autoimmunity, causing direct thyroid damage, impacting protein binding of thyroid hormone, or altering thyroid hormone activation, metabolism, and excretion [49].

Bexarotene and mitotane lead to overt central hypothyroidism, with subnormal free T4 levels and inappropriately normal thyrotropin levels, often requiring long-term hormone replacement therapy [50, 51].

Immune checkpoint inhibitors can cause central hypothyroidism due to their association with destructive hypophysitis within 1–3 months after treatment initiation, as well as primary thyroid dysfunction [52].

Metformin, the most commonly used first-line treatment for type 2 diabetes mellitus, is primarily an antihyperglycemic agent but also has pleiotropic effects on various systems and processes [53]. It appears to exert a suppressive effect on thyrotropin release without significantly affecting circulating T4 levels [54]. A similar effect is seen with glucocorticoids, dopamine agonists, and somatostatin analogs [49].

Other drugs act primarily for their iodine content inhibiting thyroid hormone synthesis through the Wolff-Chaikoff effect. It is important to note that excess iodine can contribute to thyrotoxicosis in specific patient groups (especially those with multinodular goiter), leading to the Jod-Basedow phenomenon, typically caused by amiodarone. This drug can also cause destructive thyroiditis, which is clinically presented as thyrotoxicosis, followed by euthyroidism or hypothyroidism. Drugs that are typical for their iodine excess over amiodarone are topical povidone-iodine, iodinated contrast agents, and certain over-the-counter preparations and supplementsss [49].

Other drugs enhance thyroid autoimmunity, thus causing hypothyroidism: CTLA-4 inhibitors or PD-1 inhibitors, cytokines, and interleukins are linked to either hypothyroidism (more frequently) or thyrotoxicosis after developing thyroid antibodies. Alemtuzumab, a humanized monoclonal antibody against CD52 used in multiple sclerosis, is associated with a high rate of thyroid autoimmunity, increasing the risk of autoimmune hypothyroidism or Graves' disease [55].

Protein binding of thyroid hormone, and consequently thyroid function, can also be affected by several drugs. Specifically, oral estrogen, selective estrogen receptor modulators, methadone, heroin, mitotane, and fluorouracil increase thyroxine-binding globulin, requiring higher doses of L-T4 to maintain physiological plasma levels of the hormone. In contrast, androgens, glucocorticoids, and niacin reduce thyroxine-binding globulin, necessitating lower doses of L-T4.

Finally, carbamazepine, phenytoin, valproate, and oxcarbazepine administered to patients with primary hypothyroidism may require higher L-T4 doses, likely due to a central effect on the thyroid axis, mimicking central hypothyroidism [56]. These drugs also enhance the metabolism of thyroid hormones, and specifically, phenytoin and carbamazepine displace T4 from binding proteins. Similarly, tricyclic antidepressants and selective serotonin reuptake inhibitors can influence thyroid function tests, necessitating an increase in L-T4 dosage to manage hypothyroidism [57]. These drugs, by inducing glucuronidation enzymes involved in L-T4 metabolism, may require higher doses of levothyroxine [58].

7 Clinical Practice Tips

The American Thyroid Association Guidelines on hypothyroidism recommend that patients receiving L-thyroxine treatment for hypothyroidism have their serum TSH levels assessed 4–8 weeks after starting treatment. This is particularly important for patients with multiple comorbidities or when taking medications that can affect

L-thyroxine. These medications include those that reduce the bioavailability of L-thyroxine, alter its metabolism, bind to transport proteins, or interfere with thyroid function. See Tables 2 and 3. Examples are estrogens, androgens (such as anabolic steroids), and other drugs that impact thyroid homeostasis. Furthermore, based on low-quality evidence and as a weak recommendation, they suggest, where feasible, separating levothyroxine administration from other potentially interfering

Table 2 Drugs which can alter either L-T4 absorption or thyroid "homeostasis"

Drugs	Mechanism of interaction	Recommendations
Proton pump inhibitors	Gastric juice alkalinization	Posticipate assumption by 3–4 h from L-T4
Cimetidine	Gastric juice alkalinization	Posticipate assumption by 4 h from L-T4
Sucralfate	Insoluble complex formation at gastric level	Posticipate assumption by 6–8 h from L-T4
Cholestiramine	Insoluble complex formation at intestinal level—enterohepatic recycling inhibition	Avoid concomitant use
Polystirene sulfonate	Insoluble complex formation at gastric and intestinal level	Posticipate assumption by 10 h from L-T4
Raloxifene	Undefined	Posticipate assumption by 12 h from L-T4
Simeticone	Insoluble complex formation at gastric and intestinal level	Avoid concomitant use
Ciprofloxacin	Undefined	Avoid concomitant use
TKI	Inhibition of intestinal transporters	Strict monitoring of thyroid function
Orlistat	Insoluble complex formation at intestinal level	Avoid concomitant use
Bisphosphonates (alendronate)	Physiochemical interaction at intestinal level (not well defined)	Limited data
Semaglutide (OS)	Reduction of intestinal absorption	Strict monitoring of thyroid function—change to liquid formulations of L-T4
Enteral nutrition	Reduction of intestinal absorption	Stopping enteral nutrition for 30 min before and after administering L-T4 or change to liquid formulations
Estrogens	TBG increase	Evaluate increasing of L-T4 dosage
Androgens	TBG reduction	Evaluate reduction of L-T4 dosage
Amiodarone	Hormone synthesis and metabolism interference	Strict monitoring of thyroid function
Glucocorticoids	Reduction of TSH secretion and TBG production	Monitoring of thyroid function

(continued)

Table 2 (continued)

Drugs	Mechanism of interaction	Recommendations
Rifampicin/fenobarbital	Increase in hepatic T4 metabolism	Monitoring of thyroid function
Lithium	Reduction of thyroid hormone synthesis and release	Monitoring of thyroid function
Metformin	Reduction of TSH levels	Monitoring of thyroid function
Antiepileptic drugs (AED)	Presumed central effect—increase in hepatic T4 metabolism	Monitoring of thyroid function
Antidepressant	Presumed central effect—increase in hepatic T4 metabolism	Monitoring of thyroid function
CTLA-4 inhibitors, PD-1 inhibitors, cytokines, interleukins, alemtuzumab	Develop thyroid antibodies leading to hypothyroidism or hyperthyroidism	Monitoring thyroid function

Table 3 Supplements which can alter L-T4 absorption

Supplements	Mechanism of interaction	Recommendations
Calcium salt	Insoluble complex formation at gastric level	Posticipate assumption by 2–4 h from L-T4
Iron salt	Insoluble complex formation at intestinal level	Posticipate assumption by 4–6 h from L-T4
Aluminum hydroxide	Insoluble complex formation at intestinal level	Posticipate assumption by 2–4 h from L-T4
Vitamin C	Gastric juice pH reduction	Not coingest

medications and supplements, especially those with similar effects to established interfering drugs but that have not been sufficiently studied [59].

8 Gastrointestinal Disorders and Surgical Procedures Affecting L-T4 Absorption

As mentioned earlier, both the stomach and the intestine play a crucial role in levothyroxine absorption. Therefore, impaired function in either of these organs can lead to L-T4 malabsorption. Below, we highlight the main pathologies affecting the gastrointestinal tract that often necessitate an increase in L-T4 dose to achieve euthyroidism. See Table 4.

Table 4 Gastrointestinal disorders and surgical procedures which can alter either L-T4 absorption or thyroid "homeostasis"

Gastrointestinal disorders and surgical procedures affecting L-T4 absorption	Mechanisms of interference	Recommendations
Gastroparesis	Impaired delivery of L-T4 to intestine—ehyroxine transformation in nonabsorbable compound—exposition of L-T4 to dietary components	Monitoring of thyroid function
Helicobacter pylori infection and atrophic gastritis	Gastric juice alkalinization	Eradication of HP—Monitoring of thyroid function
Lactose maldigestion and intolerance	Increased intestinal motility—impaired enterohepatic recycling	Lactose free diet—Monitoring of thyroid function
Celiac disease	Intestinal mucosal damage—increase of water in intestinal lumen	Gluten free diet—Monitoring of thyroid function—Increase of L-T4 dosage
Giardia lamblia infestation	Intestinal mucosal damage	Eradication of the parasite infestation
Cystic fibrosis (pancreatic insufficiency)	Steatorrhea and impaired enterohepatic circulation	Restore pancreas function—Monitoring of thyroid function
Liver cirrhosis	Impaired bile production and excretion—increasing of TBG	Monitoring of thyroid function
Malabsorptive bariatric procedures	Shortening of intestinal surface—accelerated intestinal transit	Monitoring of thyroid function
Sleeve gastrectomy	Beginning of PPIs and micronutrients that interfere with L-T4	See specific drug recommendation

8.1 Gastroparesis

Gastroparesis is a condition characterized by delayed gastric emptying, causing typical symptoms such as fullness after meals, pain, nausea, vomiting, etc. This condition is primarily caused by diabetes and secondarily by stomach surgery, infections, and drugs such as narcotics and antidepressants. In some cases, it is idiopathic. It can affect L-T4 absorption through multiple mechanisms: increased exposure of thyroxine to dietary components, gastrointestinal motility disorders, impaired delivery of drugs to the bowel, and the transformation of thyroxine into a nonabsorbable compound in the stomach [60].

8.2 Helicobacter pylori *Infection and Atrophic Gastritis*

Helicobacter pylori infection affects about half of the global population, with prevalence varying based on location and sanitation standards [61]. Bugadici et al. demonstrated that this infection contributes to the increased need for levothyroxine, and there is a risk of iatrogenic thyrotoxicosis if the previous dose of thyroxine is maintained after pathogen elimination. The infection can progress to atrophic gastritis, leading to reduced acid secretion (achlorhydria), thus impairing L-T4 absorption [62].

8.3 *Lactose Maldigestion and Intolerance*

In lactose maldigestion and intolerance, lactose hydrolysis does not occur, leading to sugar accumulation and consequently attracting water into the intestinal lumen, which alters the intestinal content. This altered content can bind with L-T4, preventing absorption, or may increase intestinal motility, reducing the time L-T4 is exposed to the absorbent surface [63]. Lactose maldigestion may also be associated with intestinal bacterial overgrowth, altering microbiota composition thus impairing the enterohepatic recycling of T4 [20].

8.4 *Celiac Disease*

Celiac disease is often associated with Hashimoto's thyroiditis as part of polyendocrine autoimmune syndromes. An increased need for L-T4 supplementation has been observed, particularly in atypical celiac patients who are noncompliant with a gluten-free diet, due to intestinal mucosal damage. Furthermore, reduced absorption may be due to the presence of undigested food and the subsequent increase in water in the intestinal lumen [64]. Virili et al. [65] observed an increased need for L-T4 supplementation in patients with celiac disease, even in its atypical presentation, which could be prevented by a gluten-free diet. They found that the therapeutic dose of L-T4 for celiac patients should be increased by nearly 50% to achieve euthyroidism.

8.5 *Giardia Lamblia Infestation (Parasitic Disease)*

Although sporadic in Western countries, infestation with Giardia lamblia can cause L-T4 malabsorption due to inflammatory mucosal damage and protozoan-induced apoptosis of intestinal mucosal cells, associated to a disruption of intestinal tight junctions and increased permeability [66].

8.6 Pancreatic Insufficiency, Cystic Fibrosis, and Liver Cirrhosis

Cystic fibrosis often leads to pancreatic insufficiency and steatorrhea due to reduced lipase secretion. This is associated with impaired enterohepatic circulation, increased hormone elimination through fecal losses, and altered L-T4 absorption [67]. Benvenga et al. [68] highlighted the link between liver cirrhosis and an increased requirement for L-T4. This is due to impaired bile production and excretion, which affects the intestinal absorption of L-T4 through the physiological enterohepatic circulation. Additionally, liver cirrhosis leads to higher levels of serum thyroid-binding globulin (TBG), and the increased TBG-T4 binding further raises the daily requirement for L-T4.

8.7 Bariatric Procedures

Clinical studies have shown a decrease in L-T4 requirements for the majority of patients undergoing bariatric procedures (e.g., laparoscopic Roux-en-Y gastric bypass, biliopancreatic diversion, laparoscopic adjustable gastric banding, and sleeve gastrectomy). This is most likely due to the correlation between weight reduction and the subsequent change in levothyroxine dosing, with a minor impact from a postoperative altered thyroid hormone homeostasis and the reversal of impaired levothyroxine pharmacokinetics typically seen in obesity [69]. Conversely, the increased need for oral levothyroxine that often occurs after sleeve gastrectomy is primarily due to the use of proton pump inhibitors (PPIs) and micronutrients that can interfere with L-T4 absorption. Additionally, these patients often experience accelerated gastric emptying, which can impair the disaggregation and dissolution of L-T4 tablets. An increased L-T4 dosage may also be required after malabsorptive bariatric procedures due to the shortening of the intestinal surface and accelerated intestinal transit. For the same reason, short bowel syndrome, which results from congenital malformations or diseases requiring surgical resection of the small intestine, is associated with impaired L-T4 absorption [70].

Questions for Self-Assessment

1. *Which of the following medications most significantly impairs levothyroxine absorption?*

   (a) Metformin
   (b) Calcium carbonate
   (c) Enalapril
   (d) Sitagliptin

   Correct answer: (b) Calcium carbonate

2. *What is the main mechanism by which carbamazepine alters levothyroxine effectiveness?*

   (a) Reduced renal clearance
   (b) Induction of hepatic metabolism
   (c) Inhibition of T4-to-T3 conversion
   (d) Competition for TSH receptor binding

   Correct answer: (b) Induction of hepatic metabolism
3. *A patient stabilized on LT4 develops elevated TSH after starting cholestyramine. What is the likely explanation?*

   (a) Increased thyroid hormone production
   (b) Reduced hepatic clearance
   (c) Decreased intestinal absorption of LT4
   (d) Enhanced peripheral conversion of T4 to T3

   Correct answer: (c) Decreased intestinal absorption of LT4

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Cardiovascular Effects of GLP-1 Analogues

Lucio Amoresano

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Chapter Introduction: What You Will Learn in This Chapter
In this chapter, you will explore the cardiovascular benefits of glucagon-like peptide-1 (GLP-1) analogues in the treatment of type 2 diabetes mellitus (T2DM). GLP-1 analogues have emerged not only as effective glycemic control agents but also as potential therapies for reducing cardiovascular risk in diabetic patients. This chapter highlights the key findings from major clinical trials such as LEADER, SUSTAIN, REWIND, and SELECT, which support the cardiovascular advantages of GLP-1 therapies. Additionally, the chapter delves into the mechanisms by which GLP-1 analogues provide cardioprotection and their potential role in managing both metabolic and cardiovascular aspects of T2DM.

Key Points
- Cardiovascular risk in T2DM and the role of GLP-1 analogues in mitigating this risk
- Insights from landmark clinical trials (LEADER, SUSTAIN, REWIND, SELECT)
- Mechanisms of action for GLP-1 analogues beyond glycemic control
- Future directions in the research and clinical use of GLP-1 analogues

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Learning Objectives
By the end of this chapter, you should be able to:

- Understand the cardiovascular benefits of GLP-1 analogues in patients with type 2 diabetes mellitus (T2DM).
- Evaluate key clinical trial data that demonstrate the cardioprotective effects of GLP-1 analogues.
- Identify the mechanisms through which GLP-1 analogues improve cardiovascular outcomes.
- Discuss the potential implications for GLP-1 therapy in patients with T2DM and associated cardiovascular risks.

Definitions
- *GLP-1 (Glucagon-like peptide-1)*: A hormone that regulates blood glucose levels by enhancing insulin secretion, inhibiting glucagon release, and slowing gastric emptying. It plays a crucial role in glucose metabolism and is a target for diabetes therapy.
- *Cardiovascular Risk*: The probability of experiencing adverse cardiovascular events such as heart attacks, strokes, or heart failure. In patients with T2DM, the risk is elevated due to the metabolic disturbances caused by the disease.
- *MACE (Major Adverse Cardiovascular Events)*: A composite outcome often used in clinical trials to measure the impact of treatments on cardiovascular health. It typically includes death from cardiovascular causes, nonfatal heart attacks, and nonfatal strokes.
- *Epicardial Fat*: Fat tissue located around the heart, which is thought to contribute to the development of atherosclerosis and other cardiovascular conditions.

1 Introduction

Cardiovascular disease remains a significant concern for patients with type 2 diabetes mellitus (T2DM) due to their increased risk of adverse cardiovascular events. Over the years, various pharmacological agents have been developed to manage T2DM and mitigate cardiovascular risk. Among these agents, glucagon-like peptide-1 (GLP-1) analogues have emerged as promising therapeutic options, offering not only glycemic control but also potential cardiovascular benefits. This chapter explores the cardiovascular effects of GLP-1 analogues and combination therapies, incorporating insights from recent clinical trials and research studies.

2 Cardiovascular Effects of GLP-1 Analogues

In recent years, glucagon-like peptide-1 (GLP-1) agonists have emerged as a promising class of drugs for the treatment of type 2 diabetes mellitus (T2DM). Beyond their established role in improving glycemic control, accumulating evidence

suggests that GLP-1 agonists possess unique cardioprotective properties. This has sparked considerable interest in exploring their potential benefits in reducing cardiovascular risk among patients with T2DM.

GLP-1 agonists exert their effects through the activation of the GLP-1 receptor, which is expressed in various tissues, including the pancreas, gastrointestinal tract, and cardiovascular system. While initially developed for their glucose-lowering effects, studies have increasingly revealed their favorable impact on cardiovascular outcomes, independently from glycemic control (h).

One of the hallmarks of GLP-1 agonists is their ability to improve cardiovascular function through multiple mechanisms. These include enhancing myocardial contractility, reducing inflammation, oxidative stress, and apoptosis, and improving endothelial function. Additionally, GLP-1 agonists have been shown to modulate lipid metabolism, reduce blood pressure, and inhibit platelet aggregation, all of which contribute to their cardioprotective effects [1].

Major data are available for Liraglutide, Semaglutide, and Dulaglutide and we will briefly analyze their main clinical trials:

2.1 LEADER Trial: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results

The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial aimed to evaluate the cardiovascular outcomes associated with liraglutide treatment in patients with type 2 diabetes mellitus (T2DM). Here are the key findings from the trial: The trial enrolled over 9000 patients with type 2 diabetes and high cardiovascular risk. Liraglutide treatment demonstrated a significant reduction in major adverse cardiovascular events (MACE) compared to placebo [2]. This reduction indicates a substantial cardioprotective effect of liraglutide in patients with type 2 diabetes and high cardiovascular risk. In addition to the cardiovascular benefits, the LEADER trial also showed improvements in glycemic control among patients treated with liraglutide compared to those receiving placebo.

The results of the LEADER trial highlight the potential of liraglutide as a therapeutic agent for improving cardiovascular outcomes in patients with type 2 diabetes mellitus, beyond its effects on glycemic control.

2.2 SUSTAIN Trial: Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) trial investigated the cardiovascular outcomes associated with semaglutide treatment in patients with type 2 diabetes mellitus. Here are the key findings from the trial: The trial included over 3000 patients with type 2 diabetes and high

cardiovascular risk. Semaglutide therapy was associated with a decreased risk of major adverse cardiovascular events (MACE) compared to placebo. Additionally, there was a significant reduction in cardiovascular death with semaglutide treatment. Semaglutide treatment demonstrated improvements in glycemic control and reduction in body weight compared to placebo [3].

The results of the SUSTAIN trial underscore the potential of semaglutide as a therapeutic agent for reducing cardiovascular risk and improving glycemic control in patients with type 2 diabetes mellitus.

2.3 REWIND Trial: Researching Cardiovascular Events with a Weekly Incretin in Diabetes

The REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial aimed to evaluate the cardiovascular outcomes associated with dulaglutide treatment in patients with type 2 diabetes mellitus. Here are the key findings from the trial:

The trial enrolled over 9000 patients with type 2 diabetes, including some without prior cardiovascular disease. Dulaglutide treatment resulted in a reduction in the risk of major cardiovascular events (MACE) compared to placebo. Moreover, there was a significant decrease in the risk of stroke with dulaglutide therapy. Dulaglutide treatment demonstrated improvements in glycemic control and reduction in body weight compared to placebo.

The results of the REWIND trial highlight the potential of dulaglutide as a therapeutic agent for reducing cardiovascular risk and improving glycemic control in patients with type 2 diabetes mellitus [4].

One of the most important factor that these data indicate is that the cardioprotective effects of GLP-1 analogues are not solely dependent on glycemic control but involve additional mechanisms that contribute to reducing cardiovascular risk independently of glucose levels.

Another important study that supports the independence from glucose control is the SELECT trial:

The SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial was conducted to assess the cardiovascular outcomes of semaglutide in individuals who were overweight or obese but did not have diabetes. The trial included over 17,000 participants who were overweight or obese but did not have diabetes mellitus.

Semaglutide treatment resulted in a significant reduction of 33% in the relative risk of major adverse cardiovascular events (MACE) compared to placebo. This reduction indicates a substantial cardioprotective effect of semaglutide in individuals without diabetes who are overweight or obese.

In addition to the cardiovascular benefits, the SELECT trial also demonstrated a remarkable reduction of 59% in the relative risk of developing type 2 diabetes

mellitus (T2DM) among participants treated with semaglutide compared to those in the placebo group. This finding suggests a potential role for semaglutide in preventing the onset of T2DM in individuals at risk due to overweight or obesity.

The results of the SELECT trial underscore the potential of semaglutide as a therapeutic agent not only for improving cardiovascular outcomes but also for preventing the development of type 2 diabetes in individuals who are overweight or obese [5]. These findings contribute to the growing body of evidence supporting the broader utility of GLP-1 receptor agonists beyond the treatment of diabetes mellitus.

3 Possible Mechanisms of Cardioprotection

One of the main mechanisms is the reduction of oxidative stress and inflammation through the activation of the GLP-1 receptor in cardiac tissues. GLP-1 analogues also decrease apoptosis of cardiac cells and improve endothelial function, thereby contributing to the protection of the heart against cardiovascular diseases. Additional mechanisms include the modulation of the renin-angiotensin-aldosterone system and the reduction of thrombosis risk [6].

Moreover recent data showed how GLP-1RA can reduce also epicardial and pericoronary fat, in particular: A study conducted by Iacobellis et al. investigated the effects of liraglutide on epicardial and pericoronary fat in patients with type 2 diabetes and obesity. The results showed a significant reduction in epicardial and pericoronary fat after 6 months of treatment with liraglutide [7].

Another study, conducted by Nishio et al., examined the effects of semaglutide on epicardial fat in patients with type 2 diabetes and obesity. The results highlighted a significant reduction in epicardial fat after 6 months of treatment with semaglutide [8].

A study conducted by Liu et al. assessed the effects of dulaglutide on epicardial and pericoronary fat in patients with type 2 diabetes. The results demonstrated a significant reduction in epicardial and pericoronary fat after 12 months of treatment with dulaglutide [9].

These studies suggest that GLP-1 analogues may have positive effects on reducing epicardial and pericoronary fat, potentially contributing to the reduction of cardiovascular risk in patients with type 2 diabetes and obesity. However, further research is needed to confirm these findings and fully understand the mechanisms involved.

4 Oral Semaglutide

Currently, specific evidence regarding the cardioprotective effect of oral semaglutide is still under evaluation. As oral semaglutide is one of the latest additions to the class of GLP-1 analogues, research on its cardiovascular effects may not be as extensive as that on other drugs in the same class.

However, it is important to note that oral semaglutide has demonstrated efficacy in improving glycemic control and reducing body weight in patients with type 2 diabetes, as demonstrated in the phase III PIONEER clinical trials [10]. These studies have also provided some data on cardiovascular safety, but further research is needed to comprehensively evaluate the effects of oral semaglutide on cardiovascular health.

5 Future Directions and Clinical Implications

5.1 Other GLP-1 RA

Not every GLP-1RA showed cardioprotective effects, for example, Exenatide and Lixisenatide, so it remains unclear whether this is a class effect or specific to individual drugs [11, 12].

It is important to emphasize that the lack of demonstration of cardioprotective effects in these GLP-1 analogues may be due to various factors, including study design, duration of follow-up, and specific characteristics of the patients included in the trials. Further research may be necessary to fully understand the cardiovascular impact of these medications and identify any patient subgroups that may derive greater benefit from their administration.

6 Conclusion

GLP-1 analogues and combination therapies represent innovative approaches to managing T2DM and mitigating cardiovascular risk. The robust evidence from clinical trials underscores their potential to improve patient outcomes by addressing both metabolic and cardiovascular aspects of the disease. As our understanding of these therapies continues to evolve, they are likely to play an increasingly prominent role in the comprehensive management of T2DM and associated cardiovascular complications.

Questions for Self-Assessment

1. *What was the main finding of the LEADER trial regarding liraglutide's effects on cardiovascular risk?*

   (a) Liraglutide had no impact on cardiovascular outcomes.
   (b) Liraglutide significantly reduced major adverse cardiovascular events (MACE).
   (c) Liraglutide increased the risk of cardiovascular events.
   (d) Liraglutide only improved glycemic control but had no effect on cardiovascular events.

   Correct answer: (b) Liraglutide significantly reduced major adverse cardiovascular events (MACE).

2. *Which GLP-1 analogue was shown to reduce epicardial and pericoronary fat in patients with T2DM and obesity?*

   (a) Exenatide
   (b) Liraglutide
   (c) Sitagliptin
   (d) Insulin

   Correct answer: (b) Liraglutide
3. *What was the primary outcome of the SELECT trial?*

   (a) Semaglutide improved glycemic control in patients with type 1 diabetes.
   (b) Semaglutide reduced the risk of major cardiovascular events (MACE) in overweight or obese individuals without diabetes.
   (c) Semaglutide had no effect on cardiovascular risk.
   (d) Semaglutide was shown to increase cardiovascular risk in obese patients.

   Correct answer: (b) Semaglutide reduced the risk of major cardiovascular events (MACE) in overweight or obese individuals without diabetes.

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Insulins, Technologies, and Telemedicine

Elisa Cipponeri, Laura Vitale, Ilaria Milani, and Rosario Caruso

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Chapter Introduction: What You Will Learn in This Chapter
In this chapter, we explore the evolving landscape of insulin therapy, cutting-edge technologies, and the growing role of telemedicine in managing diabetes. We will delve into how advances in insulin delivery systems, such as insulin

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pumps, smart pens, and continuous glucose monitors (CGMs), are transforming patient care and outcomes. Additionally, this chapter discusses the integration of telemedicine in diabetes management, focusing on how remote monitoring and virtual consultations are reshaping the relationship between patients and healthcare providers.

This chapter connects to the broader theme of innovative healthcare delivery and personalized medicine, emphasizing how technology is improving both the efficiency and accessibility of diabetes management.

Key Points

- Overview of insulin therapies and delivery technologies.
- The role of continuous glucose monitoring (CGM) and its integration with insulin pumps.
- The impact of telemedicine on diabetes management, particularly in remote areas.
- The potential benefits and challenges of using technology for personalized care.
- Future trends in diabetes care through technological innovations and virtual healthcare.

Learning Objectives

By the end of this chapter, readers will be able to:

- Understand the advances in insulin delivery systems and their impact on diabetes management.
- Learn about the role of continuous glucose monitoring (CGM) and its integration with insulin pumps.
- Identify the benefits and challenges of telemedicine in the management of diabetes.
- Evaluate the potential future technologies in insulin therapy and telemedicine.
- Discuss the implications of technology on patient adherence and quality of life.

Definitions

- *Insulin Pumps*: Small, computerized devices that deliver insulin continuously throughout the day and night. They are an alternative to multiple daily injections and can provide more precise control over blood glucose levels.
- *Continuous Glucose Monitoring (CGM)*: A system that tracks glucose levels continuously throughout the day and night, providing real-time data that can be used to adjust insulin doses or other treatments. It can also alert patients to fluctuations in glucose levels.
- *Telemedicine*: The use of *telecommunication technologies* to provide remote healthcare services, including consultations, monitoring, and management of patients' conditions, often through *video calls*, *mobile apps*, or other digital platforms.
- *Smart Insulin Pens*: Devices that allow patients to track their insulin doses, automatically calculate the correct dosage, and sync data with apps for better management and feedback on treatment adherence.

1 Thyroid Disorders and Type 1 Diabetes: What Is the Common Denominator?

Thyroid disorders and type 1 diabetes mellitus are two closely associated conditions. The NHANES III study reported a higher prevalence of thyroid diseases (TD) in US subjects with diabetes compared to those without diabetes, particularly among those with positivity for antithyroid peroxidase antibodies (TPOAbs) [1].

People with type 1 diabetes (T1D) develop thyroid disorder (TD) at an earlier age compared to the general population, and its onset is associated with a more aggressive presentation of TD and poorly controlled diabetes in pediatric patients with T1D [2].

Among individuals with T1D, there is a higher risk of two- to fourfold, respectively, in women and men, compared to the general population, of developing hypothyroidism, with the risk of onset depending on the duration of diabetes [3].

The sole association between autoimmune thyroid disease (AITD) and type 1 diabetes fits within the context of type 3 polyglandular autoimmune syndrome. Additionally, there are other variants of APS that always include thyroid disorder associated with other endocrinopathies (e.g., APS 1-2-4).

The simultaneous onset of autoimmune hypothyroidism and T1D often leads to hypoglycemia due to decreased insulin requirement and increased insulin sensitivity. Glucose intolerance accompanies autoimmune hyperthyroidism in 50% of patients. In APS3, circulating organ-specific antibodies are present in each of the component diseases and usually precede clinical disease; however, unlike anti-islet antibodies, antithyroid antibodies can be present for decades without the disease manifesting [4].

In light of the frequent coexistence between T1D and TD, major scientific societies have advocated for screening programs for TD in individuals with T1D, especially due to the effects of TD on glycemic metabolism: hypothyroidism may be associated with increased risk of symptomatic hypoglycemia, whereas hyperthyroidism alters glucose metabolism, potentially leading to deteriorated metabolic control. Therefore, according to the British Thyroid Association, the American Diabetes Association (ADA), and the International Society for Pediatric and Adolescent Diabetes (ISPAD), thyroid autoimmunity and thyroid function tests should be conducted at the time of diagnosis, repeated in case of clinical symptoms of suspicion, and thyroid function tests should be repeated annually to promptly identify thyroid hormone alterations and intervene accordingly [5–7].

2 Diabetes and Insulins

Although diabetes has been a known condition for about 3500 years (accounts of hyperglycemic and polyuric states have been found since the time of Ancient Egypt), until 100 years ago, there was no effective treatment for it other than

Table 1 Pharmacokinetics of insulins

Type of insulin	Onset time	Peak time	Duration of action
Intermediate acting			
NPH insulin	1–3 h	5–8 h	18 h
Long acting			
Glargine	1.5 h	No peak	24 h
Glargine U300	6 h	No peak	24–36 h
Detemir	3–4 h	6–8 h	24 h
Degludec	30–90 min	No peak	42 h
Ultra-long acting			
Icodec	–	≈16 h	196 h
Basal insulin FC (BIF)	–	≈96 h	408 h
Rapid acting			
Lipro	10–15 min	1–2 h	3–5 h
Aspart	10–15 min	1–3 h	3–5 h
Glulisine	10–15 min	1–2 h	2–4 h
Ultrarapid acting			
Faster insulin aspart	3 min	1.5–2.2 h	5 h
Lispro aabc	2 min	1–2 h	4.6 h
Ultra-ultrarapid acting			
Biochaperone Lispro (BCLIS)	≈5 min	45–90 min	3–6 h
Ultrarapid lispro (UrLi)	1 min	57 min	5–6 h

abstaining from the intake of carbohydrates and simple sugars. The current standard treatment revolves around the use of a multi-injection "replacement" therapy with synthetic analogs of insulin with long- and short-acting durations; scientific and technological progress has allowed the production of insulin types with different pharmacokinetics and various administration systems for increased safety, flexibility, and ease of use. Since the discovery of the first insulin in 1921, pharmacological research has made significant strides, all aimed at creating formulations that can meet criteria such as safety, flexibility, low risk of hypoglycemia, glycemic stability, and a pharmacokinetic profile as closely matched as possible to that of physiological insulin secretion by pancreatic beta cells.

The insulins available on the market today are divided into slow and ultraslow analogs of insulin, as well as rapid and ultrarapid analogs (Table 1).

2.1 Slow-Acting Insulin Analogs

The history of slow-acting insulin analogs begins in the 1930s with HC Hagedorn's discovery of zinc-protein insulin. Subsequently, NPH insulin was produced, which was the most commonly used slow-acting insulin for diabetes treatment for a long time, despite its effect lasting around 12–18 h, with a pronounced peak effect—and

consequent risk of hypoglycemia—and often insufficient efficacy to cover the entire day [8]. Efforts soon focused on developing long-acting insulin analogs with a high degree of reproducibility. In the 21st century, the advent of glargine insulin has changed the pharmacokinetics of slow-acting insulins, allowing for approximately 24-h insulinization with minimal peak and less variability compared to NPH insulin [9].

The second slow-acting analog, insulin detemir, was introduced in 2005. Insulin detemir has a duration of action of up to 18–20 h, requiring, in some cases, twice-daily administration [10].

Recent technological and scientific advancements have led to the development of molecules with even longer duration of action. Insulin degludec (IDeg) is a slow-acting analog characterized by numerous modifications of the primary structure and enrichment of the preparation with phenol and zinc, allowing the molecule to have an action lasting more than 24 h [11].

There is also a new, more concentrated formulation of IGlar (Glargine 300 U/mL) available. The higher concentration allows for a slower release of the molecule from the injection site, with a flatter action profile and a more prolonged effect compared to IGlar 100, reaching a duration of up to 30 h at steady state [12]. This latest generation of slow-acting insulins has further reduced the risk of hypoglycemia, especially during the night hours.

2.2 New Ultra-Long-Acting Insulins

Ultra-long-acting insulins have recently revolutionized the pharmaceutical market. Icodec insulin is an ultra-long-acting basal insulin with a half-life of approximately 7 days, requiring once-weekly dosing. Created by replacing three amino acid residues and adding an acylated fatty acid chain, it can bind stably but reversibly to albumin, has lower affinity for the insulin receptor, reduced receptor-mediated clearance, and is less susceptible to enzymatic degradation [13].

Its safety has been demonstrated in the ONWARD clinical program: in type 2 diabetes, it has been statistically superior (in studies ONWARD 1, 2, and 3) and non-inferior (ONWARD 4) to Degludec and Glargine insulin in reducing glycated hemoglobin and rates of hypoglycemia; ONWARD 6 trial was the first to focus on type 1 diabetes and compared a basal bolus regimen with Degludec and Aspart to weekly Icodec in combination with Aspart boluses: the results showed non-inferiority in glycemic control (reduction in HbA1c) but with a higher rate of hypoglycemic events (although in a low-incidence context in both study arms) [14, 15]. Icodec would be advisable for patients with poor adherence to multi-injection therapy to improve adherence and reduce diabetic ketoacidosis events due to its prolonged action. Not to be overlooked is the improvement in quality of life due to the reduction in the number of injections required; its approval by the EMA and its introduction to the European market are expected shortly.

Basal Fc (BIF) insulin is an innovative single-chain insulin variant with an IgG2-type Fc domain; it ensures a long half-life by exploiting the mechanism of metabolic recycling of immunoglobulins through the FcRn receptor, a process that physiologically maintains stable serum levels of IgG [16].

Currently in phase 2 of study, it promises an effect comparable to existing slow-acting analogs in terms of glycemic control, but with a prolonged duration of action that appears to extend up to 10 days. Particularly in patients with type 1 diabetes, weekly BIF injection has shown, after 26 weeks of treatment, glycemic control that is not inferior to insulin Degludec, with a comparable safety profile [15].

2.3 Rapid Insulin Analogs

Since the 1980s, the introduction of single-component porcine insulins followed by recombinant human insulin contributed to reducing allergic reactions and immune-mediated lipoatrophy associated with porcine insulin therapy. This allowed for intensifying therapeutic regimens while maintaining a certain degree of safety. In 1996, Lispro insulin was the first rapid analog to be introduced to the market. The amino acid composition allows Lispro insulin to peak at 90–100 min (versus 150 min with Humulin R) after administration and return to basal levels within 5 h [17].

Aspart insulin is a rapid analog of human insulin. It is absorbed more quickly after subcutaneous administration, reaching peak levels more rapidly (at 40/60 min) and returning to baseline within 4/6 h. In the two major randomized controlled trials conducted on subjects with type 1 diabetes, it has been shown to improve postprandial glycemia control and demonstrate non-inferiority in controlling glycemic fluctuations throughout the day and HbA1c levels compared to the control group [18]. Similarly, Glulisine has an onset of 15–20 min and a peak at 60–120 min, with a pharmacokinetic profile and clinical indications quite similar to Lispro and Aspart, from which it differs due to its shorter duration of action (2–4 h) [19]. The advantage of using rapid analogs lies in the fact that they can be administered shortly before meals, providing better alignment between postprandial glycemic peak and insulin peak, while their shorter duration of action minimizes the risk of postprandial hypoglycemia.

2.4 New Ultrarapid Insulin

The first "ultra-rapid" insulin, Fiasp (Faster Aspart), was approved by the FDA for use in the United States on September 29, 2017. A meta-analysis of the pharmacokinetics and pharmacodynamics of six trials comparing faster insulin aspart with insulin aspart in patients with T1D demonstrated an onset of action at 4.9 min post-administration (vs. 11.2 min) and an earlier offset (12 min earlier) compared to

insulin aspart [20]. Clinical evidence of efficacy and safety currently supports its consideration as a viable therapeutic option, especially in patients with type 1 or 2 diabetes who would benefit from the shorter latency time from a social and lifestyle standpoint. In fact, Fiasp allows for subcutaneous injection just 2 min before a meal. Moreover, compared to other rapid-acting insulins on the market, it more closely mimics the curve of naturally produced human insulin in nondiabetic individuals, resulting in a more "physiological" activity [21].

On the other hand, BioChaperone technology aims to enhance well-established insulins that have been off-patent for years with the goal of producing new drugs for the market, not simply restyling existing ones but with actual improvement in diabetes therapy. The term "chaperone" evokes a sense of protection, of accompaniment: indeed, in this new preparation, described as a molecular system for the release of therapeutic proteins, a kind of "protective cap" consisting of polymers, oligomers, and small organic compounds is proposed to wrap around proteins such as insulin and protect them from enzymatic degradation or interaction with other compounds, thus modifying their effects in the body and especially their pharmacokinetic profiles [22]. In a double-blind study published in 2018, the pharmacokinetics and pharmacodynamics of BioChaperone technology with Lispro, Aspart, and faster insulin aspart, administered via insulin pump, were investigated, demonstrating a better prandial insulin secretion curve compared to aspart and a faster return curve to baseline values compared to faster insulin aspart [23].

2.5 New Formulations

One of the primary hurdles in multi-injection insulin therapy lies in the necessity of subcutaneous injection to achieve a therapeutic effect (pain from puncture, time commitment, and social impact such as interruption of ongoing activities for therapy administration). Pharmaceutical research has endeavored to overcome this obstacle by proposing formulations with various routes of administration, not all of which have been successful. In 2006, the first system for inhaled insulin powder administration was introduced to the market but later withdrawn due to concerns about a potential increase in pulmonary neoplasms (attributed to insulin's mitogenic action) [24].

Currently, only one inhaled insulin formulation is available, albeit limited to the American market, called Technosphere. It is a recombinant human insulin designed to release insulin at the alveolar level, where it is absorbed into the systemic circulation. A randomized, multicenter, open-label Phase 3 study in T1D demonstrated that its prandial use via Gen2 inhaler resulted in lower HbA1c levels compared to subcutaneous Aspart insulin, along with a lower rate of hypoglycemia and less weight gain in patients. The most common side effects are attributed to the drug's local action, such as cough and throat irritation. However, in a meta-analysis, patients using inhaled insulin reported a difference in FEV1 spirometry of −0.031 L compared to the control group, with a reduction that was slowly progressive in the first 6 months until stabilizing within 2 years.

This formulation could still be a useful solution for treating hyperglycemia in patients with T1DM and T2DM, especially because it addresses common obstacles in insulin-naive patients with needle phobia or concerns about weight gain.

Alternative formulations to the injectable route currently under study include oral, transdermal, gastric, intestinal, and intraperitoneal routes.

The oral route of administration is undoubtedly the most convenient, but the true advantage lies in achieving insulin absorption directly into the portal circulation, similar to the physiological mechanism. Since insulin is a peptide hormone, its oral absorption is impeded by gastric pH and enzymatic degradation. To overcome this problem, several techniques have been experimented with:

- Encapsulation of insulin in capsules resistant to acidic gastric pH but degradable in the basic intestinal environment, where the capsule can release insulin-loaded micropatches. Once adhered to the intestinal lumen wall, these micropatches can transport the hormone through the epithelium (e.g., ORMD-0801 and Capsulin).
- Technologies aimed at facilitating insulin absorption through the gastric mucosa, such as I338, a slow analog co-formulated with sodium caprate, an absorption enhancer, while still addressing the issue of poor bioavailability [25].

Regarding the gastric route of administration, in 2019, a groundbreaking innovation called the Self-Orienting Millimeter-scale Applicator (SOMA) was presented in Science. Inspired by the self-orienting capabilities of the leopard tortoise (Stigmochelys pardalis), researchers developed an ingestible, self-orienting millimeter-scale applicator—a capsule loaded with insulin and equipped with a needle protected by a carbohydrate disc. This capsule has the ability to self-orient so that it adheres with the base to the gastric surface. The acidic gastric environment dissolves the protective disc, allowing the needle, triggered by a micromolecule, to inject insulin through the mucosal layer.

The gastric mucosa, with a thickness of 4–6 mm, is better suited for this use compared to the thin intestinal wall and appears to tolerate this application well. In a clinical trial involving pigs, no micro- or macroscopic gastric lesions were observed in animals where the SOMA was implanted directly. This experimentation demonstrated a consistent and gradual insulin absorption through this route of administration, with promising results that could make it a viable method for delivering other active principles. It should be noted that the SOMA only functioned in vivo on an empty stomach, and the dose of insulin deliverable varies depending on volume, formulation type, and stability [26].

Another goal of pharmaceutical research in the field of diabetology has been to more closely mimic the physiological relationship between portal and peripheral insulin and to reduce side effects such as the risk of hypoglycemia, weight gain, and insulin resistance associated with peripheral administration. Two formulations have been developed for this purpose and are outlined below.

Insulin peglispro is a molecule consisting of a chain of polyethylene glycol covalently bound to lysine B28 of insulin lispro, with hepatic preference due to its large hydrodynamic size. Although promising on paper (a phase 3 study showed greater reduction in HbA1c compared to Glargine), it was withdrawn from the market in

2015 because it induced increased hepatic transaminases, triglyceride synthesis, and rates of hepatic steatosis [25].

The Hepatic-Directed Vesicle (HAD) insulin, currently in the experimental phase, involves a delivery system that transports insulin along with a specific liver-directed molecule (HTM) within a double-layered phospholipid membrane. It allows for both a more invasive (subcutaneous) and less invasive (oral) route of administration, aiming to mimic the physiological portal passage of insulin before entering the peripheral circulation. Regarding its mechanism of action, in vivo results support the hypothesis that HDV-I functions by stimulating hepatic glucose absorption and/or glycogen storage in insulin-deficient animals, thereby reinstating the liver as one of the key metabolic modulators of glucose metabolism. As for clinical outcomes, a study conducted on pancreatectomized dogs demonstrated how HDV normalized glucose curves during the Oral Glucose Tolerance Test (OGTT) compared to control OGTT curves (in healthy dogs). Regarding safety, a 28-day study on the toxicity of subcutaneous HDV in rats revealed no clinically significant results, nor any noteworthy laboratory or histopathological findings [27].

Finally, another interesting breakthrough is the development of true "smart" insulins, known as glucose-sensitive insulins: these are insulins whose activity or bioavailability depends on blood glucose levels. Under euglycemic conditions, the insulin assumes a "pseudo single chain" structure that is inert; however, in the case of hyperglycemia, it adopts a double polypeptide chain structure, which is the active form. This formulation would allow for the elimination of the risk of hypoglycemia or overtreatment [28].

Several formulations have been patented with this aim, not all successful. To develop a valid product of this kind, it is necessary to have:

- A sensitive system that is significantly altered within a narrow range of blood glucose levels.
- A glucose-binding and/or reactive molecule.
- A rapid response system, as glycemic fluctuations can be very quick.
- The drug must be suitable for basal or bolus use.

Numerous compounds have been proposed for these formulations, such as albumin, aldehyde, monoboronated glargine, etc. In 2023, an article was published proposing a glucose sensor membrane composed of a hydrophilic side containing PBA (phenylboronate) and a hydrophobic side associated with a membrane stabilizer (polystyrene). This system was then made more efficient by elongating the polymer chain of the hydrophilic side, thus increasing the compound's sensitivity to glucose. In vitro experiments were conducted by incorporating this system into simulated body fluids (SBF) and fetal bovine serum (FBS), where this double membrane demonstrated some sensitivity and responsiveness to glycemic variations [29].

This area of research appears promising, especially for the potential elimination of the problem of hypoglycemia, although it faces a long and obstacle-filled road ahead. The problem will be fully resolved only when it becomes possible to engineer beta cells of the pancreas from stem cells, but this project will still require several years of work [28].

3 Continuous Glucose Monitoring Systems (CGM)

3.1 What Are They?

The optimization of glycemic control is essential to prevent both acute and chronic complications of type 1 diabetes (T1D) [30, 31]. Blood glucose monitoring plays a fundamental role in diabetes management, and in recent years, it has seen significant advancements. This has led to a gradual shift from traditional self-monitoring of blood glucose (SMBG) to continuous glucose monitoring (CGM). With the improved glycemic control offered by continuous glucose monitoring systems, most clinical guidelines now recommend CGM as the preferred option for glucose monitoring among individuals with type 1 diabetes (T1D), regardless of age [32, 33].

Continuous glucose monitoring (CGM) systems are divided into two types: real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) [34]. Although both share similar underlying technology and the ability to provide trend arrows for glucose, the two systems have key differences. rtCGM systems transmit glucose values to a receiver (usually an insulin pump or a cell phone), providing real-time information and offering customizable alarms for high/low glucose levels or predictive alarms for hypoglycemia. Additionally, they can be used either standalone or integrated into insulin delivery systems, such as sensor-augmented pump therapy (SAP) or automated insulin delivery (AID) pump systems.

In contrast, isCGM systems continuously measure glucose levels and record readings every 15 min; however, to view glucose levels, the user must scan the sensor with a reader or smartphone application. Glucose threshold alarms are available in a simplified form in the second generation of isCGM (FreeStyle Libre 2, Abbott Diabetes Care) [35].

3.2 Which Benefits?

The continuous glucose monitoring (CGM) systems: rtCGM and isCGM, allow for the assessment of new variables in the treatment of diabetes mellitus. In 2019, an international consensus was established providing standardization of parameters detected by CGM systems, thereby unifying therapeutic targets across different patient groups [36].

The most significant data include the percentage of readings and time per day within the target glucose range (TIR, 3.9–10.0 mmol/L, 70–180 mg/dL), time above range (TAR), and time below range (TBR). The TAR can be further divided into TAR level 1 (>180 mg/dL) and TAR level 2 (>250 mg/dL), and similarly, the TBR into level 1 (<70 mg/dL) and level 2 (<54 mg/dL). Mean glucose, estimated hemoglobin A1c (i.e., the glycemic management indicator, GMI), coefficient of variation (CV), and standard deviation (SD) can also reflect glycemic control.

The therapeutic guidelines of the American Diabetes Association recommend CGM usage for at least 70% of the time along with a CV target equal to or less than 36% [37].

The same recommendations for nonpregnant adults establish that the target levels for hemoglobin A1c should be <7% (53 mmol/mol), TIR >70% with TBR <4%, but less stringent targets can be applied to frail individuals or those at high risk of hypoglycemia. The use of metrics derived from CGM, namely, time in range (TIR), time above range (TAR), and CGM average glucose, represent valuable tools in assessing the management of individuals with type 1 diabetes in clinical settings and correlate with HbA1c [38].

It has been demonstrated that the use of CGM improves TIR and reduces time in hypoglycemia. In particular, rtCGM provides an absolute increase of 7% in TIR, largely by reducing TAR and hypoglycemia compared to isCGM. On the other hand, isCGM, compared to SMBG systems, helps reduce hypoglycemia among people with T1D with target HbA1c, while among those with target HbA1c, it reduces hypoglycemia and increases TIR [39].

Similarly, the transition from isCGM systems to rtCGM systems results in a decrease of approximately 0.5% and an increase in TIR of 10.0%, thus providing plausible hypotheses regarding the protective effect against the onset of long-term complications. It has also been demonstrated that the beneficial effects of CGM systems are more pronounced, especially among individuals with T1D with HbA1c >64 mmol/mol (>8%) [40]. Indeed, this underscores the indication for individuals with suboptimal metabolic control.

3.3 Therapeutic Indications

Currently, therapeutic indications for CGM application are subject to guidelines provided by leading international diabetes societies. Particularly, according to the guidelines of the American Diabetes Association, the use of CGM devices should be considered early in the diagnosis of diabetes requiring insulin management. Presently, the use of CGM systems allows for close monitoring of glucose levels with insulin dose adjustments and lifestyle modifications. Conversely, discontinuation of CGM use is associated with deterioration in glycemic control, hence continuity in the use of such devices should be ensured [41].

4 Smart Pens

4.1 What Are smart MDI systems?

The last 100 years of insulin history have witnessed significant developments in insulin formulations as well as in devices for their administration. In particular, in December 2017, the FDA approved the first smart insulin pen [42]. The advent of pen caps and smart pens has further changed the approach to insulin therapy. Pen caps are devices that fit on top of insulin pens and can send information about the

time of injection and insulin quantity to an app. Then there are 'connected insulin pens', which are reusable pens that record and send information about the time and amount of insulin administered to an app that integrates this with diabetes management reports. 'Smart MDI systems', also known as 'smart insulin pens' (SIP), are refillable pens that integrate data from continuous blood glucose monitoring systems with information on insulin therapy management parameters (such as the insulin-to-carbohydrate ratio, insulin sensitivity factor, etc.) to suggest optimal insulin doses and optimise therapy [43].

4.2 Which are the benefits of smart MDI systems?

According to the Food and Drug Administration (FDA), Smart MDI systems have the ability to facilitate diabetes management by improving patient care and reducing errors associated with incorrect insulin administration (such as double dosing or therapy omissions) [44], they enhance patient therapeutic education and improve their quality of life [45].

In addition, it has been demonstrated that the greater the adherence between meal bolus and its intake, the higher the Time in Range (TIR) in adult and pediatric subjects with type 1 and type 2 diabetes undergoing multi-injection insulin therapy [46].

The Smart Insulin Pens (SIPs) assist patients in calculating insulin boluses based on the carbohydrates they decide to consume, the glucose value detected by the CGM system, and individualized insulin therapy settings, taking into account any insulin still active from previous boluses [47], thus enabling patients to estimate a more precise and accurate bolus.

4.3 Therapeutic Indications

The new insulin pens, given their undeniable advantages in optimizing insulin therapy, can be easily extended to the entire population with diabetes undergoing insulin therapy. However, they are particularly suitable for certain categories of people with diabetes, such as:

- When initiating insulin therapy and there are concerns about hypoglycemia and/or excessive weight gain.
- In cases of recurrent hypoglycemia or hypoglycemia unawareness.
- Individuals with poorly controlled diabetes requiring frequent unscheduled diabetes clinic visits.
- Those experiencing psychological distress due to glycemic variability.
- Situations where intentional or unintentional bolus omissions are frequent.
- Among individuals who struggle with insulin bolus calculations.
- Including children, the elderly, and pregnant women.

To fully utilize their potential, careful and thorough patient education on the proper use of Smart Insulin Pens (SIPs) and the settings of smart pens and any associated CGM systems is essential [48].

5 AID Systems: Automatic Insulin Delivery

5.1 What Are AID Systems?

The automatic insulin delivery systems, also known as closed-loop systems or "artificial pancreas," are transforming the management of type 1 diabetes. These systems consist of an algorithm that responds to real-time glucose sensor levels, automatically modulating insulin delivery through an insulin pump (Fig. 1).

Although insulin pumps and CGMs improve glycemic control, neither standalone nor integrated therapy (SAP) reduces the management burden as they require frequent adjustments of insulin therapy by patients to integrate glucose data provided by CGM with insulin infusion modulation by the insulin pump [49]. In automatic insulin delivery (AID) systems, an algorithm processes continuously detected glucose data from the CGM and automatically adjusts insulin delivery by the insulin pump based on the glucose parameter detected by the CGM. The advantage of these closed-loop systems, sometimes referred to as "artificial pancreas," is not only to improve glycemic control by reducing hypoglycemia and hyperglycemia but also to reduce the burden of diabetes management, consequently enhancing the quality of life for individuals with diabetes.

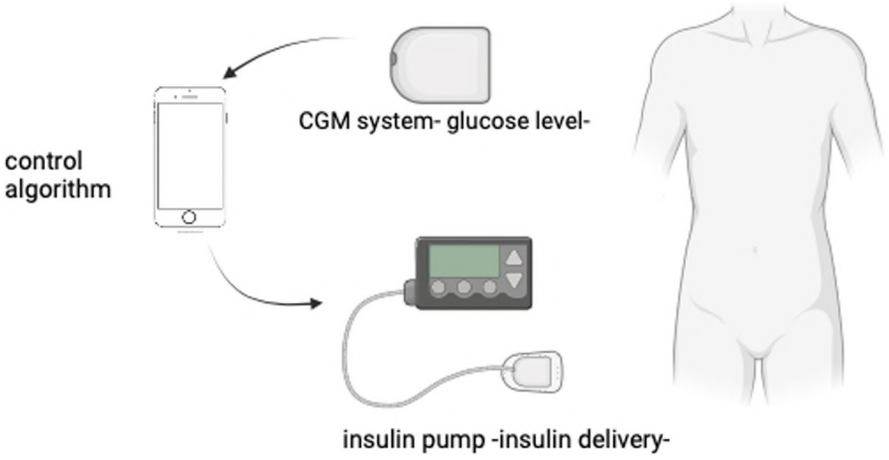

Fig. 1 AID systems. https://BioRender.com/huhsrci

5.2 The Main Control Algorithms Currently in Use

Since 1970, when Pfeiffer and colleagues experimented with the first AID system, several research groups have progressively developed algorithms capable of automatically adjusting insulin delivery every 5–10 min based on glucose readings provided by CGM. The aim of research in this field is to mimic insulin secretion as closely as possible to physiological pancreatic function. Currently, the main algorithms used by AID systems are three: Proportional Integral Derivative (PID), Model Predictive Control (MPC), and Fuzzy Logic. The PID model modulates insulin delivery based on the proportional component, which indicates the deviation of measured glucose from the target, the integral component, which evaluates the area under the curve between measured and target glucose, and the derivative component, which takes into account the rate of change of measured glucose [50].

MPC algorithms rely on forecasting glucose trends and consider CGM-measured glucose levels, insulin boluses administered, any delays in insulin absorption, as well as daily and postprandial glucose level variability [51].

The fuzzy logic system involves modulating insulin delivery based on rules reflecting the reasoning of an expert diabetologist.

The most advanced AID systems currently available are hybrid closed-loop (HCL) systems, where the control algorithm adjusts basal insulin delivery rates, but users must administer prandial insulin boluses for optimal control, although some systems can correct minor errors in meal bolus estimation [52, 53].

5.3 Do It Yourself (DIY) Systems

The do-it-yourself (DIY) closed-loop movement began with the hashtag "#WeAreNotWaiting" in 2013, initiated by a group of individuals with type 1 diabetes (T1D) and their families, tired of waiting for regulatory approval bureaucracy associated with new developments. The movement aims to develop do-it-yourself Artificial Pancreas Systems (APS) that connect the three components of AID systems (insulin pump, CGM, algorithm) by incorporating an open-source algorithm not subject to regulation by regulatory authorities [51].To date, the three main open-source systems available are Loop, OpenAPS, and AndroidAPS. The iOS Loop (Tidepool Loop), developed by the nonprofit organization Tidepool, became the first FDA-approved DIY algorithm.

5.4 Which Benefits?

DIY systems improve time in range (TIR) and reduce time spent in hyperglycemia without increasing hypoglycemia [54].

Furthermore, DIY systems contribute to a greater reduction in glycated hemoglobin (HbA1c) compared to multiple daily injection therapy associated with RT CGM [55]. Furthermore, DIY systems contribute to a greater reduction in glycated hemoglobin (HbA1c) compared to therapy with integrated systems alone (SAP—Sensor Augmented Pump) [56, 57].

A growing body of qualitative research on HCL systems reports a range of benefits for users, including reassurance and reduced anxiety, improved sleep, and "time off" from diabetes demands [58]. However, despite the numerous benefits on the quality of life of people with diabetes, there are still limitations related to the physical bulkiness of the systems, trust in algorithmic therapeutic choices, as well as alarms and connectivity issues [59].

It is always important to clarify expectations about HCL systems from the outset to avoid disappointment and promote long-term use and optimal outcomes [60].

5.5 Therapeutic Indications

Given the undeniable advantages of AID therapy, the therapeutic indications for this type of treatment can be extended to the entire population with type 1 diabetes, including those with recent diagnoses. In this category of people with diabetes, it has been demonstrated that early initiation of technologies improves and sustains long-term glycemic control, thereby likely reducing the risk of diabetes-related complications [61, 62]. Additionally, tight glycemic control from the onset of the disease in people with T1D can contribute to preserving beta-cell function [63]. The potential benefits of early initiation of insulin therapy using AID systems include long-term glycemic control, long-term acceptance of the device, and particularly advantageous therapeutic management, especially during school-age years [64].

6 The Future of Technology

6.1 Systems with Simplified Meal Announcement

As of today, all HCL systems require an estimation of the carbohydrates consumed with the meal. The more accurate the estimation, the better the system can function, resulting in optimal glycemic outcomes. However, precise carbohydrate counting poses a challenge for individuals with diabetes, both in mathematical terms and in terms of food composition [65].

In order to simplify the burden of carbohydrate counting, an algorithm has been designed to allow for a qualitative rather than quantitative estimation of the meal being consumed: in other words, the individual with diabetes, in the iLet Bionic Pancreas algorithm (Beta Bionics), announces the meal in

semiquantitative terms (larger or smaller portions than usual). The "bionic pancreas" has been shown to be safe and effective in glycemic control in a 13-week study published in 2022 [66], in which there was a reduction in HbA1c of 0.5% compared to standard therapy. These data have made it possible for FDA approval for commercialization [67].

6.2 Fully Closed-Loop Systems with Ultrarapid Insulin

The ultimate goal of AID technology is a fully closed-loop system, where the algorithm automatically determines both basal and bolus insulin requirements without the need for user intervention. However, a limitation for the full effectiveness of this technology is currently represented by the action time of insulin analogs. To date, new rapid-acting insulin analogs, such as Fiasp (Novo Nordisk) and Lyumjev (Eli Lilly), have shown only modest overall benefits compared to standard insulin analogs when applied in HCL systems [68, 69].

6.3 Fully Closed-Loop Bi-Hormonal Systems

By placing hormone replacement therapy at the center of type 1 diabetes treatment, bi-hormonal systems are born, in which the main hormones whose secretion is compromised in people with T1DM, such as amylin and insulin, are administered [51]. Insulin reduces hyperglycemia, while amylin reduces postprandial hyperglycemia by delaying gastric emptying. Another hormone frequently associated with insulin in bi-hormonal pancreas systems is glucagon. Glucagon reduces hypoglycemia by stimulating the hepatic release of glucose in response to decreasing blood glucose levels. Systems with both glucagon and insulin have been shown to reduce both hyperglycemia and hypoglycemia compared to conventional insulin pump therapy. To date, the only dual-hormone system with CE marking commercialized in the Netherlands is the Inreda system (Inreda Diabetic, Goor, Netherlands) [70]. However, to date, one of the main disadvantages is related to the instability of glucagon (lasting 24 h), which requires daily replacement of the glucagon vial. To address this drawback, chemically stable synthetic analogs of glucagon have been developed, such as dasiglucagon, which offer promising preliminary results [71].

Dual-hormone systems with pramlintide and insulin have been shown to improve postprandial hyperglycemia compared to a single-hormone closed-loop system based only on insulin [72]. Currently, the disadvantages of pramlintide are related to gastrointestinal side effects and the need for a separate pramlintide infusion pump; however, a co-formulation of insulin and pramlintide is under development [73].

7 Digital and Technological Solutions

Telemedicine is defined as the set of electronic systems that enable the provision of remote services in the healthcare sector. These services are increasingly accessible and offer various advantages, such as greater flexibility in accessing healthcare services, remote monitoring of clinical conditions, rapid transmission of data between patient and healthcare provider, tools for self-management, and reduction of stigma associated with the disease [74]. It is indeed important to destigmatize diabetes in social settings such as schools and workplaces [75]. In treating diabetes, using digital tools through smartphones and tablets allows for the adoption of various communication methods, such as email, video, and applications, in addition to the use of devices for glucose monitoring. Thanks to Digital and Technologies Solutions (DTS), communication has been revolutionized, making information more accessible and addressing ethnic, racial, and social disparities in healthcare delivery, thereby improving people's quality of life [76–78].

The use of DTS plays a crucial role in promoting patient engagement. By proving educational programs and health promotion, DTS encourages patients to self-monitor various clinical parameters, such as glucose levels, glycated hemoglobin, blood pressure, weight, diet, and physical activity, through the use of applications and online platforms [79]. This approach supports individuals' ability to independently manage their condition, enhancing their lived experiences [79–83] and improving short-term clinical outcomes, such as glycemic control, by reducing levels of glycated hemoglobin (HbA1c) and disease-related distress [84–87]. An educational approach to patients with diabetes undergoing treatment with DTS is essential to enable them to increase their levels of self-management [82]. Promoting educational programs focusing on human factors aspects supports the adoption of treatment in healthcare organizations [88]. Education, a prerequisite to ensure a high level of quality care, must not only be tailored and designed for the individual affected by the condition but should also involve the entire family unit [89]. It is known how the caregiver can positively influence disease management, especially in individuals with low levels of health literacy. Factors such as low health literacy and associated costs represent barriers to the use of such devices in a primary care setting [90]. Recognition and management of these barriers are important to improve the utilization of technology in the management of the individual [91]; furthermore, diabetes-related technologies must carefully consider the individual needs of the patient to ensure the acceptance of the devices [76].

The integration of DTS with the community healthcare system needs to be supported by a multidisciplinary involvement that can ensure a personalized approach to the individual [80, 92]; nurses play a fundamental role in the introduction, implementation, and utilization of DTS in clinical practice [77]. People with diabetes experience improvements in health outcomes through regular interaction with healthcare providers, along with consistent self-monitoring of the disease [93]. During the transition of individuals with diabetes from pediatric to adult services, clinicians must pay particular attention, considering the impact that the disease has

on the psychosocial ambit [76]; an approach based on frequent feedback and psychological support is highly recommended [94]. Implementing DTS requires a commitment of physical, financial, and human resources. Still, it can lead to reduced healthcare costs and an improved patient management, enabling continuous monitoring in situations of chronicity or multimorbidity [80].

Several theoretical frameworks can be employed to comprehensively understand the impact of digital and technological solutions in healthcare. The Technology Acceptance Model (TAM) suggests that the adoption of technology by healthcare professionals and patients is driven by perceived ease of use and usefulness [95]. Expanding on this, the Unified Theory of Acceptance and Use of Technology (UTAUT) includes social influence and facilitating conditions, helping to explain the integration of technologies like digital health records into daily use [96]. The Health Belief Model (HBM) emphasizes individual beliefs about health conditions, which influence the adoption of technologies such as mobile health apps for diabetes monitoring by shaping perceptions of threats and the benefits of engagement [97]. Similarly, the Diffusion of Innovations Theory provides insight into how new technologies spread across different demographics, which is invaluable for assessing the uptake of innovative health solutions [98]. The Socio-Technical System Theory (STS) explores the interaction between technology and society within organizations, aiding in understanding how technological solutions could be optimized in healthcare settings to improve outcomes and user satisfaction [99]. The Chronic Care Model (CCM) focuses on creating a healthcare environment that supports effective chronic disease management through well-organized care delivery systems, aligning with the aims of digital health technologies [100]. Moreover, the Ecological Model of Health Behavior considers health behaviors as the outcome of interactions between individuals and their environments, offering a perspective on how external factors affect the utilization and effectiveness of telehealth services [101]. Collectively, these frameworks provide a robust basis for analyzing the deployment, acceptance, and impact of digital tools in healthcare, particularly in managing chronic conditions like diabetes.

Building on the existing theoretical frameworks discussed earlier, the Digital and Technological Framework (Digitech-F) introduced by Conte et al. in 2023 offers a structured approach to implementing digital and technological solutions in nursing with a potential scaling-up to the broader healthcare scenario [78]. This framework is critical for understanding the multifaceted nature of the adoption of digital and technological solutions in healthcare. It emphasizes the importance of developing specific competencies, knowledge, attitudes, and behaviors that support effective integration of DTS. The Digitech-F framework addresses several key aspects necessary for successful technology adoption in nursing. Firstly, it focuses on cultivating positive attitudes toward technology, which is crucial as these attitudes significantly influence both the adoption and effective use of digital tools. Secondly, it enhances competencies and knowledge related to digital technologies, ensuring that nurses are well-prepared to utilize these tools in various healthcare settings. This is complemented by fostering a sense of self-efficacy among nurses or other healthcare providers, empowering them to manage and utilize digital resources effectively.

Moreover, the framework promotes appropriate behavioral changes that align with digital advancements and optimize nursing practices and patient care. Digitech-F supports current healthcare demands and prepares nursing professionals for future technological advancements by integrating its foundational elements. This comprehensive approach ensures that the healthcare workforce is competent, confident, and capable in a digitalized healthcare environment, ultimately enhancing patient care quality and efficiency.

In the dynamic healthcare field, especially within contexts such as diabetes management, where digital and technological solutions are increasingly integral, the need for a theoretically driven approach cannot be overstated. Theoretical clarity is crucial when designing research or implementing new technologies to ensure that these innovations effectively address the complexities of patient care and improve health outcomes. Firstly, using theoretical frameworks ensures that healthcare innovations are based on well-established knowledge bases that predict and explain how and why certain technologies affect healthcare delivery. For instance, the TAM and the UTAUT provide insights into the factors influencing the acceptance and use of digital tools among healthcare providers and patients. These models help identify barriers to adoption and facilitate the development of strategies that enhance usability and acceptance. Secondly, applying theories like the HBM or the Ecological Model of Health Behavior helps contextualize digital tools within the broader psychosocial and environmental realities of patients' lives. These models can guide the creation of patient-centered technologies that consider individual beliefs about health and the influence of external conditions on health behaviors, which is particularly significant in managing chronic diseases such as diabetes. Moreover, the STS underscores the importance of aligning technological solutions with organizational structures and processes in healthcare settings. This alignment is critical to ensure that technological implementations do not disrupt existing workflows but enhance healthcare delivery efficiency and effectiveness. The CCM further demonstrates the value of incorporating robust theoretical frameworks into the development of DTS by focusing on creating a supportive healthcare environment. This model advocates for integrating community resources and healthcare policies that improve chronic disease management, showing how theoretical grounding can lead to more holistic and sustainable healthcare solutions. Finally, employing a structured framework like the Digitech-F, as proposed by Conte et al., illustrates the application of theoretical insights to practical implementations. This framework integrates necessary competencies, attitudes, knowledge, and behaviors that should be developed among healthcare professionals to maximize the benefits of digital and technological advancements.

Recently, the integration of Artificial Intelligence (AI) in healthcare, particularly in managing chronic conditions such as diabetes, presents a disruptive yet transformative potential [102, 103]. AI can significantly alter the landscape of healthcare delivery, making it essential for providers to understand and utilize these technologies effectively within well-defined, evidence-supported frameworks. AI technologies may disrupt traditional healthcare models by providing more precise diagnostic tools, personalized treatment plans, and real-time patient

monitoring [104]. For instance, AI can analyze vast amounts of data from continuous glucose monitors and other wearable devices to predict glucose level fluctuations and suggest precise adjustments to a patient's treatment regimen. Such capabilities enhance diabetes management by allowing more nuanced control of the condition, potentially reducing the incidence of both hypo- and hyperglycemic events. However, while the benefits are substantial, introducing AI into healthcare systems requires careful consideration and preparation. Healthcare providers must be equipped with the technical skills to use these tools and a deep understanding of how AI integrates into clinical workflows. This necessitates training and education that are grounded in theoretical frameworks that emphasize ethical considerations, data security, and the maintenance of patient–provider relationships. Again, frameworks such as the Digitech-F are vital in this context because they consider the interaction between technology and society. The implementation of AI must be approached with a clear evidence-based strategy as a standard approach to change practice, not only basing changes on commercial promises of tech companies but designing robust research to test the effectiveness of each possible solution integrated into the care plans. Real-world evidence and systematic reviews should inform the deployment of new AI tools to ensure they are both effective and safe. This evidence-based approach ensures that AI applications in healthcare are needed to provide more benefits than challenges in future solutions to current patient needs. In this scenario, healthcare providers must also be prepared to address ethical issues such as data privacy, informed consent, and the potential for bias in AI algorithms. Ethical frameworks specifically developed for AI, like those proposed by medical and technical professional organizations, should guide the deployment of these technologies.

Integrating DTS in healthcare aims to create a more efficient, effective, and patient-focused system that leverages the latest advancements in technology to improve care delivery and patient outcomes. Integrating DTS, including advanced AI applications, into healthcare practices represents a significant step forward in managing chronic conditions such as diabetes. These technologies offer the potential to enhance diagnostic accuracy, personalize treatment plans, and streamline patient monitoring to improve clinical outcomes and patient quality of life. The key points discussed in this chapter and the take-home messages are followed.

Key Points to Keep in Mind

Adoption of Theoretical Frameworks: Using theoretical frameworks like the TAM, UTAUT, and the Digitech-F is crucial when approaching DTS. These frameworks help understand and navigate the complexities of technology integration in healthcare settings, ensuring that healthcare providers and patients adopt new tools smoothly and effectively.

Patient-Centered Care: DTS enables a more patient-centered approach by allowing patients to participate actively in their own care. Technologies such as mobile health apps and continuous monitoring devices empower patients to

manage their conditions more independently and with greater awareness of their health status.

Educational and Support Frameworks: It is vital to implement educational programs that enhance the digital literacy of both patients and healthcare providers. The Digitech-F framework is an example of how specific competencies, knowledge, attitudes, and behaviors could be developed systematically to support effective technology use.

Ethical and Privacy Considerations: As AI and other digital tools become more pervasive in healthcare, addressing ethical issues related to data privacy, informed consent, and algorithmic bias is essential. Ethical frameworks developed for AI use in healthcare must guide technology deployment, ensuring that patient rights are protected and that these technologies are used responsibly.

Evidence-Based Implementation: Integrating new technologies with a robust, evidence-based strategy is important. Clinical trials, real-world evidence, and systematic reviews should form the basis of technology deployment decisions to validate the effectiveness and safety of these innovations.

Take-Home Messages

The future of healthcare involves a strategic blend of technology, ethical considerations, and continuous education.

Healthcare providers must be equipped with the necessary tools and knowledge to use new technologies effectively within their clinical practices.

Continuous evaluation and adaptation of these technologies are required to keep pace with advancements and to ensure they meet the evolving needs of patients and healthcare systems.

Questions for Self-Assessment

1. *Which of the following insulin delivery systems offers continuous insulin delivery throughout the day?*

   (a) Insulin injections
   (b) Insulin pumps
   (c) Oral insulin tablets
   (d) Insulin patches

   Correct answer: (b) Insulin pumps
2. *What is the main advantage of continuous glucose monitoring (CGM) over traditional blood glucose testing?*

   (a) It is less expensive than blood glucose meters.
   (b) It provides real-time glucose data and alerts for sudden changes.
   (c) It does not require any user input.
   (d) It is used exclusively for insulin dosing.

   Correct answer: (b) It provides real-time glucose data and alerts for sudden changes.

3. *How does telemedicine improve diabetes care?*

   (a) By replacing the need for any in-person consultations.
   (b) By providing continuous, real-time monitoring of glucose levels.
   (c) By enabling remote consultations, improving access, and increasing patient engagement.
   (d) By limiting the use of insulin therapy.

   Correct answer: (c) By enabling remote consultations, improving access, and increasing patient engagement.

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Further Readings/References

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Non-pharmacological Therapies

Nutritional Approach in Thyroid Disease: Reality and Myths to Dispel

Eliana Piantanida, Daniela Gallo, Adriana Lai, and Maria Laura Tanda

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Chapter Introduction: What You Will Learn in This Chapter

Increasingly, people with thyroid diseases, especially if chronic, are looking for complementary or alternative strategies to conventional medical therapy, aimed to improve their health status. Potential strategies include diets specifically designed for thyroid health, changes in eating habits, including the exclusion of certain foods, and the intake of supplements offered on the market and widely advertised. In trying to find answers, it is not uncommon to come across dietary misinformation. For this reason, it is essential to favor the health professional interlocutor; in this way the information regarding nutritional topics can be scientifically valid and clear, so as not to give space to the so-called "fake news."

Nowadays, it seems more important than ever to clarify the authentic role of various nutritional factors on thyroid homeostasis, dispelling opinions devoid of any scientific evidence.

We will review available data regarding the role of the main nutritional topics on thyroid health, including essential micronutrients, such as iodine and selenium, particular foods, such as cruciferous vegetables and soy products, and gluten-free diet.

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Learning Objectives
The learner will be able to describe the role of essential micronutrients for thyroid homeostasis, in particular iodine and selenium, the respective recommended daily intake levels, the usefulness and methods of iodine prophylaxis, and the indications for selenium supplementation.

The learner will also be able to provide information supported by scientific evidence regarding the impact on thyroid health of the intake of certain foods, namely, brassica vegetables and soy-based products, and elimination diet regimes, such as gluten-free diet.

Definitions
- *Chronic autoimmune thyroiditis—Hashimoto's thyroiditis*: Autoimmune thyroid-specific disease characterized by circulating thyroid autoantibodies to thyroglobulin and/or thyroid peroxidase in the presence of euthyroidism or hypothyroidism.
- *Graves' disease*: Autoimmune hyperthyroidism caused by thyroid-stimulating hormone receptor antibodies, characterized by diffuse goiter and eye involvement (Graves' orbitopathy).
- *Thyroid hormones*: Hormones secreted by the thyroid gland, represented by thyroxine (T4) and triiodothyronine (T3).
- *Goiter*: Enlarged thyroid gland, caused by proliferation of thyroid follicular cells; goiter may be diffuse or nodular.
- *Celiac disease*: Autoimmune gluten-sensitive enteropathy, which results in permanent malabsorption of nutrients in the small intestine.

1 Micronutrients

1.1 Iodine

Iodine is an essential trace element, present in the human body in minute quantities (15–20 mg), almost exclusively in the thyroid gland. Iodine directly governs thyroid hormone synthesis and release in response to TSH stimulus, comprising over 50% of their weight. Following transportation into thyroid follicular cells by the sodium-iodide symporter (NIS), iodine undergoes oxidation and binds to tyrosyl residues of thyroglobulin to form thyroid hormones. Intrathyroidal iodine is recycled through the deiodination of tyrosine residues [1, 2]. Iodine is present in soil and rocks, dissolves in rainwater, and is transported by rivers to the sea; it accumulates in algae, fish, and shellfish, but can evaporate from the sea and return to the soil with rain. Iodine content in foods varies, but is generally scarce, particularly in mountainous areas compared to coastal areas. Fish contains 74 mcg, cheeses 30 mcg, milk 15 mcg, and eggs 8 mcg of iodine per 100 g of product; iodized potatoes and carrots contain 25–50 mcg of iodine per 100 g. Availability of iodine in foods may also depend on the cooking method, for example, boiling leads to a greater reduction in iodine content.

Following absorption from the gastrointestinal tract, iodine is transported via the bloodstream to the thyroid gland, where approximately 30% is retained. The remaining iodine is predominantly eliminated through urine. Thus, urinary iodine concentration (UIC) is the most sensitive indicator of iodine intake and status. The World Health Organization recommended prophylaxis through salt enrichment as an effective and safe public health measure to prevent the negative consequences of iodine deficiency. The iodine content in iodized salt, combined with the small amount of iodine naturally present in foods, allows for the daily iodine requirement, which corresponds to 150 mcg in adults (UIC of 100–199 mcg/L). Pregnant and lactating women should consume 200–250 mcg/day of iodine to ensure normal child development. According to the World Health Organization a UIC <100 mcg/L corresponds to an insufficient iodine status, more than adequate iodine intake is indicated by a UIC of 200–299 g/L, and exceeding iodine intake is revealed by a UIC of >300 mcg/L. Notably, the recommended consumption of iodized salt does not contradict recommendations for reducing salt intake (to be limited to 4–5 g/day) aimed at preventing hypertension and cardiovascular diseases ("Less salt but iodized"). In Italy, a voluntary national iodine prophylaxis program was initiated through Law No. 55 of March 21, 2005, titled "Provisions for the prevention of endemic goiter and other iodine deficiency disorders," which mandates the sale of iodized salt in all retail establishments and authorizes its use in collective catering and the food industry. The National Coordination Group for Iodine Prophylaxis at the Ministry of Health (OSNAMI) recommended the use of iodized salt also in patients with thyroid disorders. According to the Iodine Global Network (IGN), in 2021, iodine deficiency still affected 35–45% of the global population, while 118 countries, including Italy, reached an adequate iodine intake [3–5].

The most serious consequence of iodine deficiency during pregnancy is the impairment of cognitive development in the fetus, which in the most severe form is known as cretinism. Iodine deficiency is indeed the leading cause of preventable intellectual disability worldwide [6]. Iron deficiency, which is common during the latter half of pregnancy, represents an additional risk factor for low T4 levels in areas with borderline iodine deficiency [6, 7].

In adults, mild to moderate iodine deficiency prompts thyroid adaptation through increased iodine trapping, T3 synthesis, and intrathyroidal iodine retention; urinary iodine excretion is reduced. When iodine deficiency is prolonged, normal thyroid hormone levels are maintained at the expense of increased TSH, leading to thyroid hyperplasia and goiter development because of thyrotropin hyperstimulation. Chronic thyroid stimulation can finally result in toxic nodular goiter and hyperthyroidism especially if iodine intake is subsequently increased by salt iodization. However, this increase in hyperthyroidism prevalence is transient since iodine sufficiency normalizes thyroid activity and, in the long term, reduces nodular autonomy [8]. While multifocal autonomous goiter generally develops in areas with mild to moderate iodine deficiency, Graves' disease is the most frequent cause of hyperthyroidism in iodine-sufficient areas [9]. Increased iodine intake in iodine-deficient population has also been associated with a slight rise in the prevalence of subclinical hypothyroidism and of antithyroid peroxidase and thyroglobulin antibodies [10].

Population-based studies, however, demonstrated that the transitory increase in thyroid antibodies following proper iodine prophylaxis is unrelated to clinically significant thyroid dysfunction [11, 12].

In subjects without thyroid disorders, moderate iodine intake has no significant effect on thyroid hormone levels. However, excessive iodine intake can lead to a temporary and slight decrease in circulating thyroid hormones, accompanied by a modest increase in TSH levels. Importantly, these changes typically remain within the normal range [10]. Adaptation involves several mechanisms, including a reduction in iodine organification, downregulation of NIS activity, inhibition of preformed thyroid hormone release (known as the "Wolff-Chaikoff effect"), as well as a decrease in thyroglobulin proteolysis, glucose transport, and the growth and proliferation of thyroid follicular cells [10–14]. Epidemiological data suggest that even chronic iodine excess in normal subjects does not enhance the incidence of autoimmune hyperthyroidism [11, 12]. However, iodine-induced thyrotoxicosis or seronegative hyperthyroidism might occur in several cases. Nevertheless, several cases of overt hyperthyroidism have been reported in patients with subclinical/latent Graves' disease following high iodine administration or increased dietary consumption because of an extra-substrate supply for thyroid hormone production [15].

In conclusion, normal iodine status is crucial for ensuring normal neurocognitive and organic development during fetal life and childhood, and normal thyroid function and morphology in adults.

1.2 Selenium

Selenium (Se) is an essential trace element, primarily involved in oxidative metabolism and immune functions. Its biological actions are mediated through incorporation in selenoprotein enzymes, which play diverse roles in human health [16]. Rich dietary sources of selenium include Brazil nuts (equivalent to 80 mcg/nut), meat, seafood (especially tuna), cereals, and grains. Selenium concentration in vegetables varies depending on soil selenium content. A balanced diet typically provides adequate selenium intake. Additionally, selenium-fortified foods like potatoes and onions contribute around 9 mcg/100 g. The European Food Safety Authority (EFSA) recommends a daily selenium intake of 55–70 mcg for adults and 70–85 mcg during pregnancy [17]. Currently, plasma or serum selenium concentrations are the best available indicators of dietary intake. Still, the measurement of selenoproteins, especially selenoprotein P, would be more informative on selenium status. Selenium levels ranging from 70 to 120 mcg/L are deemed sufficient, while levels approximately between 121 and 140 mcg/L are regarded as optimal. Both selenium deficiency (below 70 mcg/L) and excess (150 mcg/L or above) have been associated with increased risk of mortality and disease in humans [18]. Selenium supplementation is advised in the general population for selenium levels <70 mcg/L [17].

The thyroid gland contains the highest amount of selenium in the human body, housing at least 11 selenoproteins crucial for thyroid hormone metabolism (such thyroid peroxidase and deiodinase) and redox defense mechanisms (glutathione peroxidase (GPx) and thioredoxin reductases) [19]. A higher incidence of autoimmune thyroiditis was detected in areas with severe selenium deficiency due to a decreased activity of selenium-dependent glutathione peroxidase within thyroid cells. Since selenium-dependent enzymes have several modifying effects on the immune system, even mild selenium deficiency might contribute to developing and maintaining autoimmune thyroid diseases. In murine models of autoimmune thyroid diseases, selenium supplementation notably reduced the levels of antithyroglobulin antibodies and decreased inflammatory cell infiltration in the thyroid gland [20]. Gärtner and colleagues randomized 70 patients with chronic autoimmune thyroiditis to sodium selenite supplementation (200 mcg/day) or placebo. At 3 months follow-up, the mean decrease of thyroid peroxidase antibodies title was significantly more consistent in the supplemented group compared to the placebo group; mean TSH, free thyroxine (T4), and free triiodothyronine (T3) levels were unchanged in both groups [21]. Evidence of the effectiveness of selenium supplementation in the treatment of autoimmune thyroiditis in humans is still inconclusive. In a recent systematic review including 75 randomized clinical trials, selenium supplementation proved to significantly decrease antithyroid peroxidase (TPOAb) and anti-thyroglobulin (TGAb) antibodies at 3 and 6 months, but this effect was lost after 12 months of supplementation and evidence was low [22].

Epidemiological and intervention studies detected impaired activity of selenoproteins with antioxidative functions, higher selenium consumption, and reduced selenium absorption in Graves' disease. Calissendorf et al. observed a faster reduction of FT4 levels when selenium supplementation was associated with standard antithyroid drug therapy [23]. A large meta-analysis enrolling 796 newly diagnosed Graves' disease patients confirmed that the association of selenium supplementation with antithyroid drug treatment produced a greater reduction of thyroid hormones and TSH receptor levels [24]. However, these findings were not replicated in selenium-sufficient patients [25].

Evidence supporting the beneficial effects of selenium in patients with mild Graves' orbitopathy stems from a large randomized clinical trial performed by the European Group on Graves' Orbitopathy (EUGOGO) in which selenium supplementation significantly improved quality of life, reduced ocular symptoms, and slowed disease progression [26]. This was likely independent of baseline selenium levels. Therefore, EUGOGO guidelines recommended a 6-month course of selenium for patients with mild Graves' Orbitopathy [27].

Overall, these results support the potential use of selenium as an adjuvant measure in selenium-deficient patients with chronic autoimmune thyroiditis and Graves' disease [28–30] as well as in patients with mild Graves' Orbitopathy, regardless of their selenium status [27].

2 Goitrogenic Compounds

2.1 Cruciferous Vegetables

Cruciferous vegetables, also called Brassica, are widespread throughout the world, but in the Mediterranean basin they express the greatest biodiversity. Commonly present in our diet, this large family of vegetables includes different types of cabbage, cauliflower, broccoli, Brussels sprouts, turnip greens, but also other vegetables, less known for being part of this family, such as watercress, radish, rocket, horseradish, and mustard. Rich in water, fiber, minerals, vitamins, and omega 3, they have anti-inflammatory, detoxifying, and purifying properties. These vegetables also contain glucosinolates, some of which, following enzymatic breakdown, produce sulforaphane, phenethyl, and indolyl isothiocyanates that carry out anticarcinogenic activity, particularly with regard to breast and prostate cancer. In contrast, other substances, such as progoitrin and indolic glucosinolates, through chewing degrade to goitrogenic compounds, namely, goitrin thiocyanate and isothiocyanates, that may decrease thyroid hormone synthesis: indeed, thiocyanate is a competitive inhibitor of NIS on thyroid follicular cells and hinders intrathyroidal accumulation of iodide [31]. In an extreme and striking example, a life-threatening myxedema coma has been reported in an 88-year-old diabetic Chinese woman after several months of considerable ingestion of raw bok choy (1.0–1.5 kg daily) in the belief that it would be effective in improving glycemic control [32]. Studies published in subsequent years shed a different light on the role of Brassica vegetables on thyroid health. In a study of euthyroid volunteers, the ingestion of 400 mL of commercial kale juice per day for 7 consecutive days (thiocyanate intake 5098 mcg/L) reduced mean 6-h thyroid radioiodine uptake by 2.52%, but no change in TSH and FT4 concentrations was observed [33]. More recently, from a randomized trial including 130 healthy volunteers receiving placebo and 137 receiving a broccoli sprout beverage for 12 weeks, Chartoumpekis et al. retrospectively analyzed serum samples from a subset of 45 women, 26 receiving broccoli sprout with a daily dose of 600 mcmol of glucoraphanin and 40 mcmol of sulforaphane for 12 weeks, 19 receiving placebo. No changes in serum levels of TSH, FT4, thyroglobulin, and thyroid autoimmunity status were observed in the treatment group compared to the placebo group, proving the safety of sulforaphane-containing vegetables for thyroid health [34].

Based on current knowledge, the choice to completely abolish these healthy foods from usual diet does not appear justified. The most intriguing topic is what amount of Brassica vegetables dietary intake can adversely affect thyroid gland function or, conversely, what amount can be considered reasonable, but to date there is little data available. In the lack of scientific evidence, the best choice seems to rely on common sense, as part of a well-balanced diet, with the warning to consume these vegetables preferably cooked, since the cooking process largely deactivates the myrosinase, the enzyme that promotes the hydrolysis of glucosinolates into goitrogenic compounds.

2.2 Soy Products

Soy products have been consumed increasingly nowadays due to their favorable effects on the cardiovascular system, metabolic syndrome, and bone health; moreover, through the isoflavones they contain, namely, polyphenolic compounds also classified as phytoestrogens, soy products have proven effective in reducing the intensity and frequency of hot flashes in postmenopausal women taking at least 20 mg genistein and at least 50–60 mg total isoflavones [35]. Most soy foods consumed globally are unfermented, such as soy milk, tofu, edamame, soy nuts, and sprouts, while fermented soy foods, such as soy sauce, miso, tempeh, and natto, have a small place in Eastern ethnic cuisine. To date, there is no evidence of a supposed superiority of fermented soy foods over unfermented ones in terms of health benefits. In addition to soy foods, a large selection of supplements and products without medical prescription containing isoflavones are also marketed.

First relevant reports of the harmful effects of soy proteins on thyroid function date back to the 1950s and 1960s, when several case reports were published of goiter found in infants fed soy-based infant formula. Hydovitz reported the occurrence of goiter in an infant just over 4-month old; thyroid enlargement disappeared shortly after replacing this nutrient with whole milk [36]. By supplementing infant formula with iodine, fears raised by these case reports were dispelled. In childhood, congenital hypothyroidism is a peculiar setting. In this occurrence, infants fed soy formulas need careful monitoring of free T4 and TSH concentrations, because they may require increased doses of levothyroxine to achieve adequate thyroid hormone levels, due to the inhibition of levothyroxine intestinal absorption by soy protein [37, 38].

Goitrogenic activity of soy isoflavones has been studied in vitro and in vivo in animal models, noting that in both female and male rats, dietary consumption of genistein reduces the activity of thyroperoxidase (TPO), which is essential for the synthesis of both T4 and T3, significantly and proportionally to the quantity consumed. Furthermore, in rats on a standard diet, TPO activity is approximately 50% lower than in rats on a soy-free diet [39]. Based on this evidence, it has been speculated that dietary soy product intake may have a detrimental effect on thyroid function and may alter thyroid hormone levels, increasing the risk for hypothyroidism. Similarly, it has been proposed that a higher dose of thyroid hormone replacement may be required in hypothyroid patients who habitually consume large amounts of foods or other soy products.

EFSA Panel analyzed 11 randomized and controlled studies, for a total of 925 patients on dietary supplementation with isoflavones (40–200 mg/day), including soy extracts, protein isolates, daidzein-rich isoflavones, genistein, and red clover extract for a period ranging from 3 months to 3 years, compared with 576 controls. Based on human interventional studies, EFSA Panel concluded that consumption of isoflavone-based food supplements does not affect thyroid function in euthyroid postmenopausal women [40]. Similar conclusions were reported by the Permanent Senate Commission on Food Safety of the German Research Foundation (SKLM),

notably regarding non-risk groups, including healthy, nonpregnant, premenopausal women with an adequate iodine status. Prudentially, the SKLM recommended that isoflavone intake should not exceed 20 mg/day [41]. The meta-analysis by Otun and coworkers, which includes mainly women, but also men (in 5 of the 18 studies analyzed), shows that the intake of soy isoflavones does not cause significant changes in FT3 and FT4 levels; the slight increase observed in TSH levels does not appear clinically relevant [42].

As reported by the experts of the EFSA panel [40], in patients on levothyroxine therapy, the consumption of isoflavones could interfere with the intestinal absorption of levothyroxine, affecting the effectiveness of replacement or TSH-suppressive therapy. This potential negative effect is not an exclusive prerogative of soy, but concerns a very wide range of foods, dietary supplements, and drugs [43]. This drawback can be overcome through a sufficient time interval between soy product intake and levothyroxine consumption. In this setting, guidelines recommend taking levothyroxine with water approximately 30–60 min before breakfast or no earlier than 4 h after dinner [44].

In summary, there is no reason to give up the benefits brought by soy, because consumption of reasonable amounts of soy isoflavones (indicatively up to 80 mg/day) within a balanced diet should be considered safe in euthyroid individuals living in iodine-sufficient areas. For patients undergoing treatment, simple care in the way of taking levothyroxine allows them to benefit without risk from the favorable effects of soy on health.

3 Dietary Habits: The Gluten-Free Diet

Celiac disease (CD) is an inherited autoimmune disease of the small intestine. In genetically predisposed people, the ingestion of gluten triggers chronic inflammation that leads to damage to the mucosa of the small intestine, resulting in a reduced ability to absorb dietary nutrients. Gluten is a protein complex contained in some cereals, such as wheat, rye, barley, spelt, Khorasan wheat, and triticale, which is a hybrid between wheat and rye. Prolamins are the fractions of gluten responsible for the toxic effect in CD: gliadin is the prolamin from wheat, secalin from rye, and hordein from barley. There's no definite cure for CD, but for most people, following a strict gluten-free diet, involving not only foods, but also beverages and drugs or dietary supplement containing gluten, can help manage symptoms and promote gut healing [45]. Outside of this specific therapeutic indication, gluten-free diet is burdened by some critical issues. Gluten-free products, compared to their traditional counterparts, have lower nutritional value, are often highly processed and have a higher fat and carbohydrate content. Furthermore, the exclusive or prevalent intake of gluten-free foods carries a non-negligible risk of dietary deficiency (e.g., vitamins B and D, calcium, iron, magnesium, zinc, selenium, and copper).

CD may be associated with several organ-specific autoimmune disorders, including autoimmune thyroid diseases, particularly Hashimoto's thyroiditis.

In patients diagnosed with chronic autoimmune thyroiditis, the prevalence of CD is estimated to range between 2% and 7.8%; furthermore, relative risk of CD was found to be ten times higher than in the general population, namely, 3% versus 0.33% [46]. Epidemiological data of the frequent association between CD and Hashimoto's thyroiditis led researchers to consider the gluten-free diet as a therapeutic tool for thyroid patients. In patients suffering from CD and Hashimoto's thyroiditis, some studies checking the potential interplay between gluten-free diet and blood concentrations of TSH, FT4, FT3, anti-TPO and anti-TG antibodies observed a decrease in anti-TPO and anti-TG antibodies, without changes in thyroid hormone levels [47]. Regarding the effect of a gluten-free diet on the autoimmune thyroiditis progression in patients without symptoms or specific histological features of celiac disease, a recent systematic review analyzed four prospective cohort studies published between 2019 and 2022, with a total of 87 female patients aged between 25 and 42 years. After a mean gluten deprivation period of almost 6 months, a steady decrease in anti-TPO and anti-TG antibodies was observed, almost reaching statistical significance; furthermore, a significant improvement in both TSH and FT4 levels was noted. The authors hypothesized that gluten deprivation, through its ability to attenuate the inflammatory state and reduce the permeability of the intestinal barrier, may limit the immune response, allowing the decrease in thyroid autoantibody titer. At the same time, a more effective absorption of some trace elements important for thyroid health, namely, iodine and selenium, would improve both the regulation of the immune response and thyroid function [48]. The results seem promising, but the data collected is numerically small and refers exclusively to the adult female population.

There is currently no conclusive evidence that a gluten-free diet in the absence of CD plays a favorable role in the thyroid health, changing the natural course of autoimmune thyroid disease or improving thyroid function. Accordingly, despite the growing interest in gluten-free diet, based on current knowledge, there is no clear indication to advise all non-celiac patients with chronic autoimmune thyroid disease to eliminate gluten from their diet. Only in diagnosed CD or documented gluten sensitivity is the gluten-free diet justified. On the other hand, we must never neglect to screen for other clinically relevant autoimmune diseases, endocrine and non-endocrine, in patients with Hashimoto's thyroiditis, with particular reference to CD, which makes it essential to modify eating habits by eliminating gluten intake in any form.

Questions for Self-Assessment

1. *For adults, the daily requirement of iodine is:*

   (a) 50 mcg
   (b) 100 mcg
   (c) 150 mcg
   (d) 200 mcg

   Correct answer: (c) 150 mcg

2. *Selenium supplementation is indicated in case of:*

   (a) Graves' disease
   (b) mild Graves' orbitopathy
   (c) moderate-to-severe Graves' orbitopathy
   (d) Hashimoto's thyroiditis

   Correct answer: (b) mild Graves' orbitopathy
3. *Intake of soy-based foods:*

   (a) promotes the progression of osteoporosis
   (b) causes a significant increase in TSH levels
   (c) promotes the development of autoimmune thyroid diseases
   (d) is not contraindicated in patients taking levothyroxine

   Correct answer: (d) is not contraindicated in patients taking levothyroxine

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Nutritional Approach in Diabetes: "OLD BUT GOLD"

Laura Folini

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Chapter Introduction: What You Will Learn in This Chapter

Metabolic diseases such as diabetes mellitus or impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) are often associated with overweight and obesity.

People with diabetes or IFG or IGT have in addition an increased cardiovascular risk.

Nutritional therapy and weight loss in overweight or obese subjects with metabolic diseases is the main therapeutic target.

In subjects with IFG or IGT who are overweight or obese, weight loss has been shown to be effective in preventing or delaying type 2 diabetes mellitus and improving main cardiometabolic risk factors (such blood pressure, lipids, inflammation, waist circumference).

In type 2 diabetes mellitus a modest weight loss improves glycemia and the main cardiovascular risk factors. A greater weight loss could improve long-term cardiovascular outcomes and mortality.

To improve glycemic outcomes most adults with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake and, additionally, to fat and protein intake.

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Learning Objectives
The learner will be able to describe the role of essential micronutrients for thyroid homeostasis, in particular iodine and selenium, the respective recommended daily intake levels, the usefulness and methods of iodine prophylaxis and the indications for selenium supplementation.

The student will be able to define metabolic diseases such as IFG, IGT, and diabetes. Define the clinical benefits (metabolic and cardiovascular) of weight loss in overweight individuals and those with metabolic disease. Define the role of nutrition in reducing cardiovascular and metabolic risk.

Definitions
- IFG: Impaired fasting glucose
- IGT: Impaired glucose tolerance

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is both underutilized as an energy source and overproduced due to inappropriate gluconeogenesis and glycogenolysis, resulting in hyperglycemia [1].

Diabetes can be diagnosed by demonstrating increased concentrations of glucose in venous plasma or increased A1C in the blood.

Diabetes is classified conventionally into several clinical categories (e.g., type 1 or type 2 diabetes, gestational diabetes mellitus, and other specific types derived from other causes, such as genetic causes, exocrine pancreatic disorders, and medications) [2].

"Prediabetes" is the term used for individuals whose glucose or A1C levels do not meet the criteria for diabetes yet have abnormal carbohydrate metabolism that results in elevated glucose levels (dysglycemia) intermediate between normoglycemia and diabetes. People with prediabetes are defined by the presence of impaired fasting glucose or IFG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) and/or, impaired glucose tolerance or IGT (2-h plasma glucose during 75-g oral glucose tolerance test OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) and/or A1C 5.7–6.4% (39–47 mmol/mol). As prediabetes is an intermediate state between normoglycemia and diabetes, it is clearly a significant risk factor for progression to diabetes as well as cardiovascular disease and several other cardiometabolic outcomes.

Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension. The presence of prediabetes should prompt comprehensive screening for cardiovascular risk factors [2].

1 Nutritional Therapy for Type 2 Diabetes Prevention

American Diabetes Association recommends referring adults with overweight or obesity at high risk of type 2 diabetes to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body

weight through healthy reduced-calorie diet and ≥150 min/week of moderate-intensity physical activity [3].

Obesity is defined by the World Health Organization as an abnormal or excessive fat accumulation that presents a risk to health [4].

BMI (calculated as weight in kilograms divided by the square of height in meters [kg/m^2]) has been used widely to diagnose and stage obesity (overweight: BMI 25–29.9 kg/m^2; obesity class I: BMI 30–34.9 kg/m^2; obesity class II: BMI 35–39.9 kg/m^2; obesity class III: BMI ≥40 kg/m^2) [5]. Despite its ease of measurement, BMI is at most an imperfect measure of adipose tissue mass and does not measure adipose tissue distribution. BMI is especially prone to misclassification in individuals who are very muscular or frail, as well as in populations with different body composition and cardiometabolic risk. A diagnosis of obesity should be made based on an overall assessment of the individual's adipose tissue mass (BMI can be used as a general guidance) and distribution (using other anthropometric measurements like waist circumference, waist-to-hip circumference ratio, or waist-to-height ratio) [6].

Several major randomized controlled trials, including the Diabetes Prevention Program (DPP) trial [7], the Finnish Diabetes Prevention Study (DPS) [8], and the Da Qing Diabetes Prevention Study (Da Qing study) [9], demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation) [10–11].

The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years [12].

Follow-up of three large trials of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: 39% reduction at 30 years in the Da Qing study [11], 43% reduction at 7 years in the Finnish DPS [8], and 34% reduction at 10 years [12] and 27% reduction at 15 years [13] in the US Diabetes Prevention Program Outcomes Study (DPPOS).

Nutrition counseling for weight loss in the DPP lifestyle intervention arm included a reduction of total dietary fat and calories [12, 14, 15].

Evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes and a variety of eating patterns can be considered to prevent type 2 diabetes in individuals with prediabetes.

Trials show that a variety of eating patterns may also be appropriate for individuals with prediabetes to reduce risk of developing type 2 diabetes [16, 17], including Mediterranean-style [18–20] and vegetarian diet [21, 22].

Evidence suggests that the overall quality of food consumed with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes [22, 23].

Moderate-intensity physical activity, such as brisk walking for 150 min/week, has shown beneficial effects in people with prediabetes [12].

Similarly, moderate-intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults. Health care

professionals are encouraged to promote a DPP-style program to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training. Furthermore breaking up prolonged sedentary time may also be encouraged [3].

People with prediabetes often have other cardiovascular risk factors, including hypertension and dyslipidemia, and are at increased risk for cardiovascular disease.

The lifestyle interventions for weight loss in study populations at risk for type 2 diabetes have shown a reduction in cardiovascular risk factors and the need for medications used to treat these cardiovascular risk factors [24, 25].

The lifestyle intervention in the Da Qing study was associated with lowering cardiovascular disease and mortality at 23 and 30 years of observational follow-up [9, 11].

2 Nutritional Therapy for Type 2 Diabetes Treatment

Obesity is a key pathophysiologic driver of diabetes, other cardiovascular risk factors (e.g., hypertension, hyperlipidemia, nonalcoholic fatty liver disease, and inflammatory state), and ultimately cardiovascular and microvascular complications.

In people with type 2 diabetes and overweight or obesity, weight management should represent a primary goal of treatment along with glycemic management.

Health care professionals should advise individuals with overweight or obesity and those with increasing weight trajectories that, in general, greater fat accumulation increases the risk of diabetes, cardiovascular disease, and all-cause mortality and has multiple adverse health and quality of life consequences. Health care professionals should assess readiness to engage in behavioral changes for weight loss and jointly determine behavioral and weight loss goals and individualized intervention strategies. Strategies may include nutrition and dietary changes, physical activity and exercise, behavioral counseling, pharmacotherapy, medical devices, and metabolic surgery.

People with diabetes and overweight or obesity may benefit from any magnitude of weight loss. Modest weight loss improves glycemia and other intermediate cardiovascular risk factors; a greater weight loss confers greater benefits, including disease-modifying effects and possible remission of type 2 diabetes, and may improve long-term cardiovascular outcomes and mortality.

Experts advise individualized initial treatment approaches for obesity (i.e., lifestyle and nutritional therapy, pharmacologic agents, or metabolic surgery) based on the person's medical history, life circumstances, preferences, and motivation.

Experts also suggest considering combining multiple approaches to achieve and maintain greatest weight loss and reduce obesity-associated health risks. Several modalities including intensive behavioral and lifestyle counseling, obesity pharmacotherapy, and metabolic surgery [26].

Among people with type 2 diabetes and overweight or obesity who have inadequate glycemic, blood pressure, and lipid management and/or other obesity-related metabolic complications, modest and sustained weight loss (3–7% of body weight) improves glycemia, blood pressure, and lipids and may reduce the need for disease-specific medications [27–29]. Greater weight loss may produce additional benefits. Mounting data have shown that >10% body weight loss usually confers greater benefits on glycemia and possibly diabetes remission and improves other metabolic comorbidities, including cardiovascular outcomes, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, adipose tissue inflammation, and sleep apnea, as well as physical comorbidities and quality of life [30–34].

Significant weight loss can be attained with lifestyle programs that achieve a 500–750 kcal/day energy deficit, which in most cases is approximately 1200–1500 kcal/day for women and 1500–1800 kcal/day for men, adjusted for the individual's baseline body weight. Clinical benefits typically begin upon achieving 5% weight loss [35, 36], and the benefits of weight loss are progressive; more intensive weight loss goals (>7%, >10%, >15%, etc.) may be pursued to achieve further health improvements if the individual is motivated and more intensive goals can be feasibly and safely attained.

Atherosclerotic cardiovascular disease (ASCVD)—defined as coronary heart disease (CHD), cerebrovascular disease, or peripheral artery disease (PAD) presumed to be of atherosclerotic origin—is the leading cause of morbidity and mortality for individuals with diabetes. Common conditions coexisting with type 2 diabetes (e.g., hypertension and dyslipidemia) are clear risk factors for ASCVD, and diabetes itself confers independent risk. Numerous studies have shown the efficacy of controlling individual cardiovascular risk factors in preventing or slowing ASCVD in people with diabetes. Furthermore, large benefits are seen when multiple cardiovascular risk factors (glycemic, blood pressure, and lipid control) are addressed simultaneously, with evidence for legacy benefits [37, 38].

For people with blood pressure >120/80 mmHg, lifestyle intervention is recommended and consists of weight loss when indicated, reducing sodium and increased potassium intake, moderate alcohol intake, smoking cessation, and increased physical activity [39].

To improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD) in people with diabetes, lifestyle modification focused on weight loss, if indicated; reduction of saturated fat and *trans* fat; increased dietary n-3 fatty acids, viscous fiber, and plant stanol/sterol; and increased physical activity are recommended [39].

The Look AHEAD (Action for Health in Diabetes) study [40–45] is a multicenter, randomized controlled trial designed to determine whether intentional weight loss reduces cardiovascular morbidity and mortality in overweight individuals with type 2 diabetes.

Intensive lifestyle intervention combining both diet and physical activity (when possible) have been shown to benefit weight loss and reduce downstream complications.

The Look AHEAD trial used partial meal replacement for weight-loss induction combined with heavily supported physical activity training (moderate-intensity, 175 min/week). Those in the intervention achieved an overall weight loss of 8.6% vs. 0.7% at 1 year, and 6.0% vs. 3.5% at 9.6 years in completers from the intervention group (vs. the control group).

In the Look AHEAD trial an intensive lifestyle intervention was associated with a greater likelihood of partial remission of type 2 diabetes compared with control group. However, the absolute remission rates were modest.

Look AHEAD trial did not show that the intensive lifestyle intervention reduced cardiovascular events in adults with type 2 diabetes and overweight or obesity; it did confirm the feasibility of achieving and maintaining long-term weight loss in people with type 2 diabetes. Approximately, 50% of intensive lifestyle intervention participants lost and maintained ≥5% of their initial body weight, and 27% lost and maintained ≥10% of their initial body weight at 8 years.

Also the incidence of all-cause mortality did not differ significantly between the two groups.

In those who achieved at least 10% weight loss, glycemic levels and other cardiometabolic risk factors improved, with reduced incidence of major adverse cardiovascular events.

3 Nutritional Recommendations and Dietary Patterns in Diabetes Management

Many diet types can be used successfully to reduce energy intake and produce weight loss A systematic "umbrella" review of published meta-analyses of studies comparing hypoenergetic diets for weight management in people with type 2 diabetes does not support any particular weight-loss diet over others (e.g., low-carbohydrate, high-protein, low-glycemic index, Mediterranean, high-monounsaturated fatty acid [MUFA] or vegetarian diets) [46]. This evidence indicates that a variety of weight-loss diets can be used equally effectively for weight management with type 2 diabetes, provided they can be followed and meet recommendations for protein, fat, micronutrient, and fiber intake.

Diets prescribed for weight loss or long-term weight-loss maintenance need to be nutritionally complete.

A wide range of carbohydrate intakes can be acceptable in diabetes management by focusing on carbohydrate quality: it is recommended to increase the consumption of fiber and reduce sugars.

Dietary fiber intake should be at least 35 g/day (4 g/1000 kJ) and intake of free or added sugars should be below 10% of total energy intake.

Foods naturally high in dietary fiber are whole grains, vegetables, legumes, seeds, nuts, and whole fruit. When choosing high-fiber foods, focus should be on minimally processed and largely intact whole grains, rather than products with

finely milled whole grains that may also have added sugars, sodium, and saturated fats. The same can be said of fruits, where whole and cut fruits are preferred over those that have been preserved in sweetened syrups, added to processed foods as a concentrate, or fruit juices. Following a low-glycemic index or -glycemic load diet can improve glycemic levels and intermediate cardiometabolic risk factors in those with diabetes. High sugar intakes, especially from sugar-sweetened beverages at intakes of ≥10% of total energy, increase body weight, fasting glucose and insulin, triacylglycerols and uric acid in people with or at risk for diabetes. High sugar intakes are also associated with increased risk of the metabolic syndrome, hypertension, gout, and CVD in people with or at risk for diabetes [47].

Scientific societies recommended consumption of foods containing primarily plant-based mono- and polyunsaturated fats, rather than saturated or *trans*-fats. This may be achieved by using non-hydrogenated nontropical vegetable oils (e.g., olive oil, rapeseed/canola oil, soybean oil, sunflower oil, linseed oil) and through the consumption of seeds, nuts, fish, and avocado, while limiting fats from meats and processed meats, butter, coconut products, or palm oil.

Recommended saturated fat intake is less than 10% total energy and total *trans*-fats intake is less than 1% total energy.

For people with type 2 diabetes with eGFR >60 mL/min/1.73 m^2 (estimated glomerular filtration rater, eGFR) a protein intake of 10–20% total energy is recommended. Higher intakes 15–20% total energy are recommended for those aged 65 years or older.

For people with moderate diabetic nephropathy (eGFR <60 but >45 mL/min/1.73 m^2) a protein intake of 10–15% is recommended.

For people with type 2 diabetes, who have overweight or obesity with eGFR >60 mL/min/1.73 m^2, a protein intake of 23–32% may be recommended in the short term in the context of weight-loss diet.

Good sources of protein in the diet are dairy and dairy substitutes, legumes with complementary whole grains, eggs, fish, poultry, and lean meat. However, high animal protein diets may exceed recommendations for saturated fat intakes (<10% total energy), with serum cholesterol concentrations and markers of blood glucose control generally lower for diets higher in protein from plants.

Higher intakes of vegetables and fruit remain a universal recommendation among food-based dietary recommendations [47].

A variety of dietary patterns emphasizing the consumption of whole grains, whole vegetables and fruit, legumes, nuts, seeds, and nonhydrogenated nontropical vegetable oils, while minimizing the consumption of meat (especially red and processed meat), sugar-sweetened beverages, sweets, and refined grains are recommended.

Dietary patterns that have best evidence from randomized controlled trials and prospective observational studies include: Mediterranean dietary pattern, Nordic dietary pattern, and Vegetarian dietary pattern.

Mediterranean dietary patterns are characterized by high consumption of vegetables, legumes, whole grains, fruits, nuts and extra virgin olive oil, moderate

consumption of fish and wine, and low consumption of red and processed meat, processed food, and added sugars.

Nordic dietary patterns are characterized by high consumption of whole grains (especially rye, barley, and oats), berries, other temperate fruit (especially apples, pears), vegetables (especially root, cruciferous), legumes, fish, nuts, and rapeseed/canola oil (as the main fat sources), and low-fat dairy.

Vegetarian dietary patterns exclude some or all animal foods, emphasizing the consumption of fruit, vegetables, legumes, and whole grains, and exclude meat, poultry, or fish. Lacto-ovo vegetarian dietary patterns include dairy and eggs, while a vegan diet excludes all animal products [47].

4 Nutritional Therapy for Type 1 Diabetes

Type 1 diabetes is the most common form of diabetes in youth, although data suggest that it accounts for a large proportion of cases diagnosed in adult life.

Observational studies suggest that in those with islet autoantibodies, factors that may increase β-cell demand including less physical activity, higher dietary glycemic index [48], and total sugar intake are associated with progression to clinical diabetes. Similar associations have not been seen in the development of autoantibodies.

In The Environmental Determinants of Diabetes in the Young (TEDDY) longitudinal study, daily minutes spent in moderate to vigorous physical activity were associated with a reduced risk of progression to type 1 diabetes in children 5–15 years of age with multiple islet autoantibodies [49].

In the Diabetes Autoimmunity Study in the Young (DAISY), in children with islet autoantibodies, progression to type 1 diabetes was associated with higher dietary glycemic index [48, 50].

Guidelines recommended individualized medical nutrition for youth with type 1 diabetes as an essential component of the overall treatment plan.

They encourage monitoring carbohydrate intake, whether by carbohydrate counting or experience-based estimation, as it represents a key component to optimizing glycemic management.

Meal composition impacts postprandial glucose excursions. Education on the impact of high-fat and high-protein meals and the adjustment of insulin dosing is necessary.

Comprehensive nutrition education at diagnosis, with at least annual updates and as needed, by an experienced registered dietitian nutritionist is recommended to assess caloric and nutrition intake in relation to weight status and cardiovascular disease risk factors and to inform macronutrient choices [51].

To improve glycemic outcomes and quality of life and minimize hypoglycemia risk, most adults with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake and, additionally, to fat and protein intake.

Although some studies [52] have not found the effectiveness of carbohydrate counting in type 1 diabetes on reducing glycated hemoglobin, others [53, 54] instead associate it with better glycemic control, although without benefit on hypoglycemic risk or quality of life.

A systematic review and meta-analysis of randomized studies that compared carbohydrate counting with general dietary evaluated the effectiveness and safety of carbohydrate counting in the treatment of adult patients with type 1 diabetes mellitus.

Meta-analysis showed that the final HbA1c was significantly lower in the carbohydrate counting group than in the control group, but the meta-analysis of severe hypoglycemia and quality of life did not show any significant differences between the groups [54].

Although carbohydrate content is the primary variable for calculation of meal insulin dose, it is well known that meals with higher content of fat and protein can cause early hypoglycemia and delayed postprandial excursion. Some adjustments in insulin dosing, including an increase in the calculated dose as well as a split dose, will improve postprandial glucose management [55, 56].

Optimizing postprandial blood glucose (PPG) levels after mixed meals that contain high fat and protein remains a challenge in the treatment of type 1 diabetes.

A systematic review and meta-analysis evaluated the efficacy of different algorithms used for dosing insulin based on counting units of high fat and high protein (HFHP) meals with the current conventional method of counting carbohydrates alone to control PPG excursions. The primary outcome was the PPG (mean and standard deviation) at 240 min. In total, 15 studies were identified and included in the systemic review, of which 12 were RCTs, and 3 studies were non-randomized trials.

The data was in favor of additional insulin doses in HFHP meals compared to the carbohydrate counting alone.

The authors conclude that insulin treatment based on fat and protein content, in addition to carbohydrate counting, is more effective than the carbohydrate counting method alone; however, further research is warranted to determine the best equation for fat and protein counting, particularly in people with multiple daily injections [57].

Questions for Self-Assessment

1. *According to the American Diabetes Association, what is the recommended goal for weight reduction in adults at high risk of type 2 diabetes participating in a lifestyle intervention program?*

   (a) At least 5% of initial body weight
   (b) At least 10% of initial body weight
   (c) At least 7% of initial body weight
   (d) Exactly 3% of initial body weight

   Correct answer: (c) At least 7% of initial body weight

2. *What was the reduction in the incidence of type 2 diabetes in the Diabetes Prevention Program (DPP) trial after 3 years of intensive lifestyle intervention?*

   (a) 27%
   (b) 43%
   (c) 58%
   (d) 15%

   Correct answer: (c) 58%
3. *Which of the following best summarizes the findings of the Look AHEAD (Action for Health in Diabetes) trial?*

   (a) Intensive lifestyle intervention significantly reduced the incidence of myocardial infarction and stroke in patients with type 2 diabetes.
   (b) The trial confirmed that intensive lifestyle changes are not feasible in patients with type 2 diabetes due to low adherence.
   (c) Although the intensive lifestyle intervention did not significantly reduce cardiovascular events, it proved effective in achieving and maintaining long-term weight loss and improving metabolic health in patients with type 2 diabetes.
   (d) Standard diabetes education led to better glycemic control and quality of life compared to lifestyle intervention.

   Correct answer: (c) Although the intensive lifestyle intervention did not significantly reduce cardiovascular events, it proved effective in achieving and maintaining long-term weight loss and improving metabolic health in patients with type 2 diabetes.

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Endocrine Management

Minimally Invasive Treatments of the Thyroid: The European Guidelines

Giovanni Mauri and Pierluigi Glielmo

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Chapter Introduction: What You Will Learn in This Chapter
Minimally invasive treatments (MIT) for benign thyroid nodules represent a rapidly evolving field within endocrinology and thyroidology. This chapter explores the development, applications, and European guidelines for these innovative procedures, offering a comprehensive look at how they compare with traditional surgical approaches.

The chapter is structured to:

- Introduce the main MIT modalities, including laser ablation (LA), radiofrequency ablation (RFA), microwave ablation (MWA), and ethanol ablation (EA).
- Explain the clinical indications and selection criteria for each treatment.
- Discuss recent European guidelines, including patient eligibility, procedural techniques, and follow-up strategies.
- Highlight safety, efficacy, and clinical outcomes based on the most recent data.

Learning Objectives
By the end of this chapter, readers will be able to:

- Understand the rationale behind the development of minimally invasive treatments for benign thyroid nodules.
- Identify the key features and mechanisms of action of RFA, LA, MWA, and EA.

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- Apply the latest European guidelines to select appropriate patients for each technique.
- Evaluate the safety, efficacy, and outcomes of minimally invasive thyroid procedures.

Definitions

- **Minimally Invasive Thyroid Treatments (MITT):** Procedures aimed at treating thyroid nodules without traditional open surgery, often guided by imaging and performed on an outpatient basis.
- **Radiofrequency Ablation (RFA):** A technique that uses high-frequency alternating current to generate heat and induce thermal necrosis of thyroid tissue.
- **Laser Ablation (LA):** A method using laser light to produce controlled tissue destruction through heat.
- **Microwave Ablation (MWA):** An energy-based ablation modality that generates heat via electromagnetic microwaves.
- **Ethanol Ablation (EA):** The injection of ethanol directly into cystic thyroid nodules to cause coagulative necrosis and volume reduction.
- **Volume Reduction Ratio (VRR):** A measurement used to assess the effectiveness of ablation treatments, representing the percentage decrease in nodule size.
- **Benign Thyroid Nodules:** Noncancerous growths within the thyroid gland, often diagnosed via ultrasound and fine-needle aspiration.

1 Introduction

The standard therapeutic approaches for benign thyroid lesions requiring intervention are surgical resection for cold nodules and either surgery or radioiodine therapy (RAI) for autonomously functioning thyroid nodules (AFTN). Minimally invasive thyroid treatments (MITT) are increasingly being considered as alternative therapeutic options for selected clinical scenarios. In non-hyperfunctioning nodules, MITT have demonstrated significant nodule volume reduction and symptom improvement, while minimizing the risk of hypothyroidism and avoiding complications associated with surgery. However, nodule regrowth may occur over time, which may require repeat interventions or surgical excision. For AFTN, radioactive iodine remains the first-line therapy, though thermal ablation (TA) may be indicated in younger patients with small AFTNs due to the higher likelihood of restoring euthyroidism and reducing radiation exposure. Notably, after nearly 20 years of clinical use, there is no evidence of TA techniques causing thyroid neoplasia [1, 2].

The increasing detection of papillary thyroid microcarcinomas (PTMCs) has led to a rise in surgical interventions. However, given the often-indolent nature of these tumors, along with the costs and risks associated with surgery, active surveillance (AS) and ultrasound-guided MITT are now proposed as alternatives to thyroidectomy for selected cases of incidental PTMC.

For recurrent cervical differentiated thyroid carcinoma (DTC), surgical resection and radioiodine therapy remain the standard of care. Nevertheless, the development of radioiodine-refractory disease, the risk of surgical complications, potential adverse effects on quality of life, and patient preferences against repeat surgeries have prompted consideration of AS and MITT for indolent DTC nodal metastases. Additionally, in cases of distant metastases that are refractory to radioiodine and not amenable to surgery, MITT may be employed as part of a multimodal therapeutic strategy.

2 Overview of MITT Modalities

MITT are typically performed under local anesthesia, with or without conscious sedation depending on the patient's preference, and are generally used for the ablation of PTMC, cervical lymph node metastases, and distant metastases when the procedure time is short. General anesthesia is preferred for the ablation of distant metastases requiring longer treatment times (over 60 min).

In specific cases at risk of complications, as to protect the skin in superficial tumors, a sterile saline or glucose solution can be injected around the target lesion to create a safety margin between the lesion and critical surrounding structures, a technique known as "hydrodissection."

MITT options include laser thermal ablation (LA), radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound (HIFU), ethanol ablation (EA), and cryoablation.

2.1 Laser Thermal Ablation

Laser is a focused beam of light energy, usually generated by a diode or a Nd:YAG source, delivered through an optical fiber into the target tissue [3–5]. The number of fibers to be inserted and the path to be followed are planned by the operator according to size and shape of the target lesion. Fibers are inserted into the target nodule at a 10-mm distance from each other, through thin and flexible 21-gauge (G) needles. Needle insertion along the major axis of the target lesion allows multiple backward re-positioning ("pullback") for multiple illuminations.

The heat-induced changes of the tissue are visible through the appearance of hyperechoic signals due to the formation of gas microbubbles. Most often, a fixed power protocol is used with LA, changing the total amount of energy delivered according to target tumor size and US modifications [6, 7].

The procedure is performed in an outpatient setting and requires 15–30 min [3–5].

2.2 Radiofrequency Ablation

An alternating electric current is applied to the target tissue via an electrode needle, causing rapid oscillation of tissue ions, which generates frictional heat in areas of high current density near the electrode. The ablation zone expands further through thermal diffusion [8, 9]. Both monopolar electrodes, which require collecting pads, and bipolar devices, which do not, are available. Additionally, short (7–10 cm) and thin (17–19 G) devices designed for use in the neck region are also available. Under ultrasound guidance, the electrode is introduced into the target lesion, and in larger lesions, the applicator is continuously repositioned using the "moving shot" technique to ensure complete ablation of the lesion. Similar to LA, the appearance of hyperechoic signals near the electrode tip signals tissue changes, while a rapid increase in tissue impedance confirms tissue necrosis [9, 10].

The procedure is typically performed in an outpatient clinic and lasts between 15 and 40 min.

2.3 Microwave Ablation

MWA utilizes high-frequency electromagnetic energy, ranging from MHz to GHz, to generate heat within tissues by causing rapid oscillation of water molecules. This method of direct heating is less influenced by the cooling effects of blood flow, allowing for larger and more uniform areas of tissue necrosis. The procedural steps are similar to those of RFA, where the probe is inserted into the lesion under US guidance, and tumor destruction is achieved through overlapping ablation zones.

MWA equipment comprises a microwave generator, a flexible coaxial cable, and an internally cooled antenna, typically housed within a 14- to 17-G needle [11–13]. The procedure is carried out on an outpatient basis and typically takes between 10 and 20 min.

2.4 High-Intensity Focused Ultrasound

Heat is generated by the conversion of acoustic into thermal energy. Ultrasonic energy, in the 20 kHz–200 MHz range, induces molecular vibration, frictional heating, and cavitation. By focusing the energy from a probe outside the patient into a small volume, tissue destruction can be achieved within the target tumor without affecting intervening structures and without needle insertion. Multiple overlapping ablation volumes may allow a complete target ablation.

A US diagnostic receiver and a generator of US waves are combined in a single cooled probe. A computerized mapping of the targeted tissue on the US screen provides safety margins for the skin, trachea, and large neck vessels [14, 15]. Care must

be taken to avoid subtotal treatment because computer-assisted control may prevent the ablation of peripheral areas close to critical structures [16, 17].

Repositioning of the patient is needed when patient motions are detected by a laser control, in order to avoid treatment of critical areas [14, 15].

The procedure is performed in an outpatient setting, and treatment duration ranges from 40 to 60 min, but large-size (>5 cm) nodules usually require multiple treatments.

2.5 Ethanol Ablation

Ethanol induces tissue destruction by causing coagulative necrosis and damage to the endothelium, leading to thrombosis of small blood vessels, ischemic injury, and permanent tissue ablation. The procedure utilizes 21–27 G needles connected to a 1–5 mL syringe filled with 95–99.9% ethanol. Small volumes (0.1–0.5 mL) of ethanol are injected slowly, depending on the lesion's size and shape, while continuous ultrasound monitoring ensures proper diffusion. Following ethanol injection, the treated area becomes echogenic on ultrasound, which can obscure the needle tip and blur the target region. After 1–3 min, the echogenic area diminishes, allowing the needle to be repositioned into any remaining untreated sections. Injections are repeated until the entire lesion is thoroughly treated. Ethanol leakage outside the lesion may occur, causing severe pain and requiring immediate cessation of the injection [18–20].

2.6 Cryoablation

Tissue necrosis is induced by significantly lowering the temperature to between −40 °C and −140 °C. Pressurized gas, usually argon, is released from the needle probe through a narrow channel at its tip, rapidly cooling the surrounding tissue through the Joule-Thomson effect. This cooling creates an "ice ball" around the target area. Probes that generate ice balls in various sizes are available, and multiple probes can be used together to shape the ablation zone to match the tumor's size. The ice ball is easily visible on CT and MRI scans and can be monitored during the procedure, though less clearly on ultrasound.

The exact mechanism of tissue injury is not fully understood, but factors such as osmotic stress, cell wall damage from ice crystal formation, and microvascular thrombosis contribute to the ablation. Cryoablation causes less disruption to tissue structures compared to heat-based methods, which may lower the risk of vascular or nerve damage, though significant complications can still occur [21, 22]. This approach is usually less painful than thermal ablation, but it requires more time, as multiple cycles of freezing and thawing are necessary to achieve effective tissue destruction.

3 Current Clinical Practice Guidelines

The Executive Committees of the European Thyroid Association (ETA) and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) commissioned development of guidelines for the treatment of benign and malignant lesions.

The guidelines consist of a series of recommendations from panels of experts. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [23], was used when rating the strength of the recommendations and the quality of evidence behind each of these.

The following coding system has been used: (a) strong recommendation indicated by 1, and (b) weak recommendation, or suggestion, indicated by 2. The evidence grading is given as follows: very-low-quality (ØOOO), low-quality (ØØOO), moderate-quality (ØØØO), and high-quality evidence (ØØØØ).

3.1 Guidelines for MITT of Benign Thyroid Nodules

Recommendation 1. In adult patients with benign thyroid nodules that cause pressure symptoms and/or cosmetic concerns and decline surgery, image-guided TA should be considered as a cost- and risk-effective alternative option to surgical treatment or observation alone (1, ØØOO).

Thyroid nodules are frequently observed in adults, with a prevalence of up to 50% in women and 30% in men based on US examinations. The majority of these nodules are cytologically benign, causing no local symptoms or requiring any treatment. However, a notable number of patients may experience discomfort from pressure, cosmetic concerns, or develop subclinical or overt hyperthyroidism due to AFTN [24–26]. As a result, many patients in European countries undergo surgery, even for benign nodules, without being offered alternative nonsurgical options [27, 28]. For these cases, EA was initially introduced as a nonsurgical treatment, followed by TA procedures, which have been performed under US guidance for about three decades. Today, TA has largely replaced EA for most thyroid lesions, except for pure cysts, due to its predictable tissue destruction [3–5]. TA is regarded as a cost-effective and low-risk option for reducing benign nodules and alleviating local symptoms, providing a less invasive alternative to surgery, and crucially, it generally avoids the development of hypothyroidism.

Recommendation 2. We recommend against the use of TA for asymptomatic lesions (1, ØØØO).

Treatment of asymptomatic nodules is generally not advised, suggesting that TA should be considered only for benign nodules that cause pressure or cosmetic concerns. Establishing a clear volume cutoff for recommending TA is complex, as symptoms and cosmetic issues are influenced by factors beyond just the size of the nodule. These include its location in the thyroid, neck circumference, and other

subjective variables that are hard to quantify [24, 29, 30]. For instance, female patients and those with thinner necks may notice cosmetic changes earlier, while most individuals with nodules larger than 30 mm, especially in the isthmus, tend to report pressure symptoms [31]. Therefore, in line with other guidelines [30], TA should primarily be considered for nodules measuring ≥30 mm that exhibit continuous growth during US follow-up, particularly in patients who begin to experience local discomfort.

Recommendation 3. Before TA of thyroid lesions, a benign cytological diagnosis is needed. A repeat FNA is suggested for cytologically benign nodules with the exception of spongiform nodules and pure cystic lesions (EU-TIRADS Class 2). A calcitonin determination should also be considered. We recommend against TA for nodules with high-risk US features (EU-TIRADS Class 5) (1, ØØØO).

Before planning TA for thyroid nodules, a benign cytological diagnosis is essential to reduce the risk of missing malignant lesions and delaying appropriate treatment. In cases of cytologically benign nodules, a repeat FNA is advisable, as follicular tumors and follicular variants of papillary thyroid carcinoma may not display high-risk sonographic features [30, 32] and carry a notable risk of false-negative cytology results [33, 34]. However, a repeat FNA can be omitted for cytologically benign spongiform and purely cystic nodules [35]. TA should be strictly avoided in nodules with high-risk US characteristics (EU-TIRADS 5) due to the significant risk of malignancy [36, 37]. Additionally, since medullary thyroid cancer may not always present with suspicious US or clear cytological findings, it is recommended to include a single calcitonin test, along with TSH, in the initial biochemical workup [3, 37].

Recommendation 4. Patients should be carefully informed before the procedure, orally and in writing, about the TA treatment options, their potential efficacy and side effects, the therapeutic alternatives, and the necessity of being compliant (1, ØOOO).

The patient must be thoroughly informed, both verbally and in writing, about several key aspects. This includes an explanation of the available management options—such as observation, TA, or surgery—along with their respective advantages and limitations. The specific details of the TA procedure, including the necessary compliance during the treatment, potential complications, and the expected reduction in nodule size, should also be communicated. It is important to clarify that complete disappearance of the nodule is uncommon, and there may be a risk of regrowth over time, potentially requiring additional TA or surgery. Lastly, the patient should understand the need for long-term follow-up to monitor the condition.

Recommendation 5. Before the TA procedure, thyroid and vocal cord function, comorbidities, and contraindications to TA treatment should be evaluated. Laryngoscopy is recommended in patients with hoarseness, previous neck surgery, or with nodules close to critical structures ("danger areas") (1, ØØOO).

For hyperfunctioning thyroid nodules, hyperthyroidism should initially be managed with antithyroid drugs, and the benefits and drawbacks of RAI therapy should

be carefully considered and discussed with the patient [38]. Conditions such as Graves' disease and toxic multinodular goiter are not suitable for TA.

Vocal cord function must be evaluated prior to TA, with laryngoscopy recommended for patients with hoarseness, a history of thyroid surgery, or nodules located near the trachea or nerve structures [39].

A detailed US examination should be performed by the operator to confirm the indication for TA, rule out any anatomical contraindications, and plan the procedure.

Clotting disorders, relevant comorbidities, and pregnancy status should also be assessed before proceeding with TA.

Recommendation 6. Local subcutaneous and pericapsular anesthesia is recommended before TA procedures. Mild conscious sedation may be considered, especially in case of HIFU treatment (1, ØØOO).

During TA, it is essential to prevent frequent swallowing and head movements. To assist with this, mild conscious sedation, such as intravenous midazolam (1–3 mg), can be administered to help keep the patient calm throughout the procedure [29, 37, 40, 41]. When large-bore needles are used in TA, local subcutaneous and pericapsular anesthesia is typically advised. Even during HIFU, local anesthesia can be useful in reducing discomfort caused by the mechanical impact of the ultrasound beam on the skin and thyroid capsule [29, 37, 40]. Local anesthesia is usually achieved by injecting a 2% lidocaine or mepivacaine solution into the skin, neck muscles, and thyroid capsule along the expected path of the needle. Monitoring vital signs such as blood pressure, heart rate, and pO2 is essential, and is mandatory if conscious sedation is used [37, 40, 41].

Recommendation 7. At the end of the procedure, clinical and US evaluation is recommended in order to rule out potential early adverse effects and define the extent of the ablated area. Patients should be instructed to present for clinical and US assessment if severe pain, local swelling, or fever occur within the first week after TA (1, ØØOO).

Applying mild compression to the neck with an ice pack can help prevent local bleeding and thermal injury to the skin. After the procedure, a clinical and US assessment is essential to detect any early complications, such as hematoma, burns, or damage to the thyroid capsule, as well as to evaluate the ablation area. The treated region typically appears mildly hypoechoic and inhomogeneous, with scattered hyperechoic spots caused by tissue vaporization [4, 37]. Doppler US can enhance the definition of the treated zone, which will show an absence of vascular signals. For a more detailed assessment, contrast-enhanced US can provide a clearer view of the loss of small vessel signals and more accurately reveal any peripheral areas that were not fully treated [42–48]. However, it is important to note that in some European countries, thyroid nodular disease is not an approved indication for the use of contrast agents with US.

Post-procedure, an anti-inflammatory drug such as ketoprofen (100 mg) may be administered parenterally to manage pain, followed by an oral painkiller like paracetamol (1000 mg twice daily) for the next 24 h. Patients should be advised to

seek clinical and US evaluation if they experience severe pain, local swelling, or fever within the first week after TA [41].

Recommendation 8. Early-term (e.g., 3 months) and intermediate-term (e.g., 6 and 12 months) clinical, biochemical, and US evaluations are recommended. Long-term follow-up monitoring is suggested, in the absence of symptoms every 1–2 years, in order to reveal regrowth (1, ØØOO).

Clinical trials have provided various recommendations for short- and long-term clinical and US monitoring schedules following TA procedures [29, 37, 40, 41]. It is generally advised that clinical, biochemical (including at least TSH measurement), and US assessments be conducted at the following stages:

(a) An initial evaluation at 3 months to assess the early effects of TA and review thyroid function.
(b) Further evaluations at 6 and 12 months to monitor nodule volume reduction and identify any residual viable areas, as the majority of nodule shrinkage is typically seen within this period.
(c) Long-term US follow-up every 1 to 2 years to track any further changes in nodule size and structure [49–53].

Extended biochemical monitoring is usually unnecessary for non-hyperfunctioning nodules, but in cases of AFTN, continued thyroid function testing is recommended. Long-term US assessments are crucial because some nodules may begin to regrow 3 to 5 years after treatment, potentially requiring additional TA or surgery [54–56]. Definitions of nodule regrowth post-TA vary, with recurrence rates after 3 years ranging between 5% and 24%. Currently, regrowth is classified as an increase in nodule volume of over 50% compared to its smallest recorded size. Factors that may predict recurrence include a larger initial nodule size, functional autonomy, insufficient energy applied during the procedure, and incomplete ablation of the nodule's edges [44–46]. When regrowth is detected in untreated peripheral areas, it is advisable to perform a second TA to prevent further volume increase and symptom recurrence [47]. Additionally, a repeat cytological analysis should be considered before retreatment, as regrowth could signal a previously undiagnosed malignancy [34, 40].

Physicians who perform thyroid US examinations during follow-up after TA procedures should be aware of the timing and characteristics of structural modifications induced by the intervention. This is to avoid misinterpretations of late, potentially worrisome, morphological changes (e.g., development of a hypoechoic lesion with intranodular calcifications) [41].

Recommendation 9. Based on direct comparison studies, and balance between efficacy and side-effects, LA and RFA are recommended as the first-line TA treatment modalities (1, ØØØO).

LA has been shown to reduce the volume of benign nonfunctioning thyroid nodules by approximately 44–52% over 6 to 36 months [57]. This technique is particularly effective in spongiform and mixed nodules compared to completely solid ones [56]. Most patients experience improvement in cosmetic concerns and local

symptoms after LA [50–52]. Major complications are rare, occurring in about 0.5% of cases, with temporary vocal cord palsy being the most significant risk—especially when treating nodules near the inferomedial portion of the thyroid lobe, known as the "danger area" [52]. Minor complications like small hematomas and skin burns are also uncommon. Overall, LA is well-tolerated, though some patients may experience transient neck pain. Significant changes in thyroid function post-treatment are rare.

RFA is another effective treatment for thyroid nodules [58, 59], achieving a mean volume reduction of 69–78% at 12 months [60, 61], and demonstrating long-term efficacy over 5 years [61]. Smaller nodules tend to respond better to RFA, with higher volume reductions observed in nodules less than 12 mL compared to larger ones [60, 61]. Like LA, as tissue structure affects the alternating current flow, spongiform and mixed nodules respond more favorably than solid ones [62, 63]. RFA also improves pressure symptoms and cosmetic appearance [62, 63]. Major complications occur in about 1.3–1.4% of patients, with most voice changes being temporary and permanent changes being very rare [64, 65]. Minor side effects include hematomas, skin burns, and transient pain. While direct comparisons with surgical treatments are limited, some studies suggest patients are more satisfied with the cosmetic outcomes of RFA compared to surgery, and RFA may offer better quality of life scores [66, 67].

When comparing LA and RFA for treating benign solid nonfunctioning thyroid nodules, both techniques show similar safety and effectiveness. Outcomes can vary based on the operator's skill and experience [68]. Some studies indicate that RFA may offer slightly greater nodule volume reduction than LA. For example, one study reported a 77.8% volume reduction with RFA versus 49.5% with LA at 6 months [69]. However, improvements in symptoms and cosmetic concerns are comparable between the two methods [70].

Recommendation 10. Based on studies to date, MWA should at present be considered a second-line TA procedure in patients who are not suitable for or decline other TA procedures, or for participants in protocolled clinical studies (1, ØØOO).

High-quality evidence for MWA is still limited. Two meta-analyses reported that MWA achieved nodule volume reductions of 74% at 6 months and 89% at 12 months [71, 72]. However, MWA appears to be associated with a higher risk of major and minor complications compared to LA and RFA, possibly due to less precise control of the applied energy and the use of larger applicators [72].

In a prospective, non-randomized multicenter study involving 1252 patients treated with either MWA or RFA, both techniques demonstrated similar effectiveness. MWA was associated with a marginally higher complication rate than RFA (7% vs. 5%, respectively) [73].

Recommendation 11. Based on its lower efficacy, higher cost, and limited reported trial evidence, as compared to RFA and LA, HIFU should be considered only for selected nodules in patients who are not suitable for or decline other TA procedures, and for participants in protocolled studies (1, ØØOO).

Research on HIFU for thyroid nodules is limited and predominantly comes from a small number of institutions, with no data available from prospective randomized trials. A 2017 review [74] analyzed six retrospective and prospective studies with follow-up periods between 3 and 12 months. This review found that HIFU treatment resulted in mean nodule volume reductions ranging from 48.8% to 68.8%. An inverse relationship was observed between the initial nodule size and the percentage of volume reduction; significant decreases exceeding 50% were achieved only in small nodules measuring 3.0 mL or less [75].

Recommendation 12. In multinodular goiters, due to lack of evidence of efficacy and the expected need of repeat treatment, TA should be restricted to patients with a well-defined dominant nodule or those who are not candidates for thyroid surgery or radioactive iodine treatment, as a palliative therapy option (1, ØØOO).

For patients suffering from compressive multinodular goiters, TA is not recommended as a substitute for surgery due to its inadequate effectiveness and the likelihood of requiring multiple treatments. Such patients should undergo thorough evaluation with CT or MRI scans to exclude the presence of intrathoracic extension or potential compression of vital structures [76]. If TA is considered in these cases, it should be limited to those with a dominant nodule who are unsuitable for surgical intervention, serving solely as a palliative option [11, 37, 42].

Recommendation 13. Because of higher cost and complexity, as compared to aspiration and EA, TA procedures are not recommended as a first-line treatment for pure or dominantly cystic thyroid lesions (1, ØØØO).

Recommendation 14. LA and RFA should be considered therapeutic options for cystic lesions that relapse after EA and for those that would remain symptomatic due to a large residual solid component (1, ØØØO).

For cystic thyroid nodules, techniques such as LA, RFA, and MWA require draining the fluid component before treatment, typically done during the same session [77]. While most studies involving these methods include both solid and cystic nodules, only a few specifically focus on cystic ones. Two prospective randomized trials comparing EA and RFA in predominantly cystic nodules found similar effectiveness at 6 months [78, 79], supporting EA as the first-line treatment for benign cystic nodules due to its lower cost.

Combining EA with RFA can improve outcomes when initial treatment is incomplete [80], and using ethanol alongside LA has been effective for treating very large cystic nodules [81, 82].

Since HIFU is noninvasive and does not allow for fluid drainage, it is less suitable for cystic lesions. Moreover, no significant studies have examined fluid removal followed by HIFU treatment. Even after drainage, residual fluid within the solid component may persist, potentially reducing the effectiveness of ultrasound therapy.

Recommendation 15. We recommend against TA as first-line treatment for large AFTN. Due to the low rate of restoration of normal thyroid function, TA should be considered only for patients who decline or are not candidates for RAI therapy or surgery (1, ØØØO).

Recommendation 16. TA should be considered in young patients with small AFTN and incomplete suppression of perinodular thyroid tissue due to the higher probability of normalization of thyroid function and the advantage of avoiding irradiation and restricting the risk of late hypothyroidism (1, ØØOO).

Recommendation 17. Treatment with a combination of LA or RFA and RAI may be considered in selected patients with large AFTN that cause local pressure symptoms in order to achieve a more rapid volume reduction and use of a lower RAI activity (2, ØØOO).

Available data on TA in AFTNs primarily originate from studies on LA [83, 84] and RFA [85, 86]. The overall mean technical efficacy—defined as the restoration of normal thyroid function along with a reduction of at least 80% in initial nodule volume—is approximately 50% at 12 months posttreatment. However, the effectiveness diminishes with increasing nodule size, making durable control of thyroid function less likely in larger nodules [85, 87]. Therefore, TA may be most suitable for patients with small AFTNs who decline or are unsuitable for RAI therapy or thyroid surgery due to iodine repletion, comorbidities, or pregnancy.

In a prospective trial involving patients with large hyperfunctioning thyroid nodules (>10 mL), those treated with RAI alone were compared to those receiving LA followed by RAI 1 month later. The combined treatment group showed a more significant and rapid improvement in local symptoms [88]. Additionally, these patients experienced greater nodule volume reduction and required significantly lower doses of administered RAI [88]. This indicates that TA could be utilized for selected large AFTNs to reduce nodule volume prior to RAI therapy [84, 88].

HIFU appears to be less effective than RAI in controlling hyperfunctioning nodules. A prospective trial comparing two cohorts treated with either HIFU or RAI found that euthyroidism at 12 months was achieved in 94% of RAI-treated patients versus 53% of those treated with HIFU [89].

3.2 Guidelines for MITT of Malignant Thyroid Lesions

Recommendation 1. Consider the use of image-guided MITT in the multimodal approach to patients with thyroid cancer (1, ØØOO).

Recommendation 2. A multidisciplinary team, which includes members with specific expertise in MITT, perform the selection of patients eligible for MITT based on the patient's clinical, demographic, and imaging characteristics (1, ØØOO).

Recommendation 3. Select the MITT modality based on involved organ(s), staging of the disease, patient characteristics and preferences, and specific competences and resources at the treating center (1, ØØOO).

The use of MITT may be considered in patients with DTC in the following conditions: PTMC, unresectable thyroid cancer, neck lymph-node recurrences of DTC, distant metastases.

Indications for image-guided MITT in thyroid malignancies should be evaluated by a multidisciplinary team including experts in both traditional and image-guided interventional treatment modalities [8].

Recommendation 4. Inform patients about MITT feasibility and its advantages and limitations in comparison with the other management strategies (1, ØOOO).

Recommendation 6. Inform patients with incidentally discovered PTMC who are suitable for AS about TA as a therapeutic alternative to immediate surgery or AS (1, ØOOO).

Recommendation 7. Inform patients with PTMC about advantages and limitations of TA in comparison with the other management options and the need of protracted clinical and US follow-up for ruling out potential locoregional recurrences (1, evidence ØØOO).

In managing PTMC, AS is an alternative to immediate surgery to reduce surgical risks and prevent hypothyroidism, considering the low likelihood of cancer progression [90]. Although direct comparisons between TA and AS are lacking, TA offers the advantage of eliminating cancerous tissue, which may be beneficial for some patients. During a 5-year period of AS, tumor growth has been observed in 12–23% of cases, with some patients—particularly younger ones—developing extrathyroidal spread or cervical metastases [91–93]. TA may also alleviate the anxiety of living with an untreated tumor that could progress and require more aggressive surgery [94].

While randomized trials comparing TA and surgery for PTMC are not available, retrospective studies provide useful insights. These studies indicate that TA and surgery have similar clinical outcomes, but TA offers benefits such as shorter procedure times, reduced hospital stays, lower costs, fewer major complications, and improved posttreatment thyroid-related quality of life [95, 96]. Meta-analyses support these findings, showing similar recurrence rates and recurrence-free survival between TA and surgery, with TA associated with significantly fewer complications (odds ratio 0.24), reduced costs, and recovery time [97].

In cases of neck recurrences of DTC, prospective comparisons between TA and surgery are lacking. However, retrospective studies indicate that RFA may provide similar recurrence-free survival rates to surgery but with fewer major complications, especially hypocalcemia, which occurs mainly in surgical patients [98, 99].

Recommendation 5. Consider the use of image-guided TA for patients with low-risk PTMC, mainly if the patient is at surgical risk, is expected to have short life expectancy, has comorbidities that need to be prioritized before thyroid surgery, or is unwilling to undergo surgery or AS (1, ØØOO).

MITT have mainly been used to treat incidentally diagnosed PTMC [100–106], with limited application in other primary thyroid tumors [101, 107, 108]. Due to the indolent nature of PTMC and the risks and costs associated with surgery, AS and MIT are considered alternative management options to thyroidectomy [90, 91, 109]. Since the initial feasibility study using laser for nonsurgical management [110], LA, RFA, and MWA have demonstrated effectiveness and safety [111, 112].

Systematic reviews and meta-analyses confirm high efficacy, showing no local tumor recurrence or distant metastases, low rates of minor complications, and very few major complications [111, 112]. In particular, in one study based on 503 PTMCs with follow-up ranging from 8 to 53 months there were neither local tumor recurrence nor distant metastases after TA [111]. Cervical lymph node metastases were detected in two patients (0.4%). There were no major complications, and minor complications (transient dysphonia, intrathyroidal bleeding, and parenchymal edema) ranged from 3.4% to 19.0% [111]. A second meta-analysis, including 715 patients with follow-up ranging from 8 to 26 months, registered complete disappearance in 57.6% of treated PTMC. Scar-like remnants, devoid of viable cancer cells at FNA, were observed in the remaining cases. Major (persistent dysphonia) and minor complications were reported in 0.7 and 3.2% of cases, respectively, with a 0.4% local recurrence rate [112].

Recommendation 8. Choose treatment modality based on specific competences and resources at the individual center, because LA, RFA, and MWA are similarly safe and effective TA techniques for low-risk PTMC (1, ØØOO).

Recommendation 9. Abstain from using EA and HIFU for PTMC treatment, due to insufficient evidence and technical limitations (1, ØOOO).

The selection of an appropriate MIT procedure—whether EA, LA, RFA, MWA, or HIFU—depends on the tumor type and location, the team's expertise, available technical resources, and patient characteristics [40].

A meta-analysis involving 1284 PTMCs compared RFA, MWA, and LA. The results showed that RFA achieved the highest rate of complete disappearance (76.2%) and the lowest recurrence rate (0.01%), although these differences were not statistically significant. Conversely, LA had the lowest complication rate (0.9%) compared to RFA (1.7%) and MWA (6.0%) [113].

EA was applied in a small series of 15 patients with PTMC. After ethanol injection, all cases demonstrated tumor shrinkage and absence of Doppler flow. No major complications, local recurrence, or nodal metastases were reported [114].

Recommendation 10. Consider MIT for palliative purposes, preferentially in the context of a multimodality approach, in patients with primary thyroid cancer, other than low-risk PTMC (2, ØOOO).

In patients with unresectable thyroid cancer, MIT can be utilized as a palliative treatment to rapidly decrease tumor burden and improve local symptoms, especially within a multimodal therapy approach [101, 107, 108].

Although data are limited, studies have reported a mean tumor volume reduction of 51% in inoperable DTCs following MIT. However, RFA may be less effective when tumors exhibit significant vascular encasement or massive calcification due to challenging access and insufficient ablation area [115]. In cases where DTC invades the airways, volume reduction rates of 81.2% and complete disappearance rates of 72.1% have been observed over a mean follow-up of 47.9 months; nonetheless, efficacy decreases notably with greater tracheal involvement [16].

LA and RFA have also been employed for managing medullary thyroid cancer in patients not suitable for surgery [116, 117]. While some case reports indicate that TA can achieve short-term local control in medullary thyroid cancer, the available evidence remains limited.

For anaplastic thyroid cancers, LA has been explored, typically providing minor short-term symptom relief without significant reduction in tumor volume [101, 107, 108]. Consequently, TA for inoperable anaplastic or medullary thyroid carcinoma yields inconsistent outcomes and should be considered only as a palliative option when no other treatments are possible.

Regarding thyroid nodules diagnosed as follicular neoplasms, TA has been reported in a few studies. In one 5-year follow-up, RFA led to complete disappearance of eight out of ten follicular lesions smaller than 2.0 cm, with the remaining two showing a 97% volume reduction; no recurrences or distant metastases were observed [118]. In another study involving six thyroid lesions with follicular cytology and negative BRAF and NRAS molecular tests, RFA was applied and followed up for 24 months. Two lesions regrew and were surgically removed, revealing a follicular carcinoma and a follicular neoplasm of indeterminate malignant behavior [2]. Therefore, surgery remains the standard of care for thyroid nodules with Bethesda IV cytology due to the risk of delayed diagnosis and potential distant metastasis in follicular thyroid cancers. TA should be reserved for patients at surgical risk who present favorable US features and negative molecular testing, serving as an alternative to clinical surveillance.

Recommendation 11. Consider MITT as an alternative option to surgical neck dissection in patients with radioiodine refractory cervical recurrences who are at surgical risk or decline further surgery (1, ØØOO).

Recommendation 14. Consider MITT only for palliative purposes in DTC recurrences with extensive lymph node involvement, central location, evidence of radioiodine uptake, and clinical and histological factors suggestive of aggressive disease (1, ØØOO).

The majority of DTCs are successfully cured with initial surgical treatment, followed, if needed, by RAI ablation [26]. Even after apparently successful treatment, recurrence can occur in the thyroid bed and/or as nodal metastases. Repeat compartment-oriented surgery is the established therapeutic approach for DTC recurrences but lymphadenectomy results in biochemical and structural remission only in some of these patients [119]. Thus, AS and MIT can be considered an alternative to surgery for selected patients with cervical DTC metastases [26].

EA has been reported as effective in local disease control in a few single-center case series [18, 120, 121].

LA was reported feasible in RAI refractory cervical DTC recurrence following cervical lymph-node dissection. A prospective trial in eight non-RAI-avid cervical recurrences demonstrated a mean volume decrease from 0.64 to 0.07 mL at 12 months, with undetectable Tg levels in 60% of cases [122]. In 46 18FDG-PET/computerized tomography-positive nodal metastases followed up for 30 months

[123], local control was obtained in 40 of 46 (86.9%) lymph nodes, with no detectable residual disease in 79% of patients.

In a retrospective study of 24 lymph node metastases of PTC treated with MWA, nearly complete disappearance was achieved with no late recurrence reported during a 32-month follow-up [124]. A prospective study of 23 cervical PTC recurrences, with an up to 18-month follow-up, demonstrated a 91% mean volume reduction at the final follow-up. Complete disappearance in 30.4% and persistence as scar-like areas in 52.2% were reported [125].

Notably, TA of thyroid cancer metastases is followed by a rapid increase of serum Tg levels during the following 48 h. After complete destruction of lymph node metastases, serum Tg progressively decreases to undetectable levels and becomes a sensitive blood marker for monitoring potential disease relapse [6, 122]. Similarly, serum calcitonin level may be used as an effective marker for monitoring the local control of medullary thyroid cancer metastases after thermal ablation of nodal recurrences [7].

Recommendation 12. Confirm the diagnosis of DTC recurrence by fine needle aspiration or core-needle biopsy before MIT (1, ØØOO).

Recommendation 13. Consider the following clinical factors as favoring MITT for DTC: cervical recurrences, a previous surgical neck dissection, presence of surgical complications, small size metastases, and limited latero-cervical lymph node involvement (1, ØØOO).

MITT are most suitable for fragile patients with limited life expectancy, prior neck surgeries, surgical complications, small metastases (<20 mm), and a limited number of affected lymph nodes (<4) in the lateral cervical regions [7, 123–126]. TA should generally be avoided, except for palliative care, in patients with extensive lymph node involvement, central neck recurrences, evidence of radioiodine uptake, or clinical and histological signs indicating aggressive disease.

The use of MITT is contraindicated when cytology suggests aggressive subtypes of thyroid carcinoma (e.g., tall cell, insular, columnar cell), imaging reveals extrathyroidal extension or multiple tumor foci, lymph node or distant metastases are present, or there are concerning molecular markers such as TERT promoter or TP53 mutations [100, 113, 127–129]. Additionally, for young patients without comorbidities, who have a higher risk of lymph node metastases and require lifelong follow-up, immediate surgery remains the preferred therapeutic approach [100].

Recommendation 15. Consider TA among the treatment options in patients with oligometastatic or oligoprogressive disease, to achieve local tumor control or pain palliation (1, ØØOO).

Follicular and, to a lesser extent, papillary thyroid carcinomas result in distant metastases in up to 10% of cases, with lung and bone representing the two most commonly involved organs [130]. Various therapy options are currently available in metastatic patients, including RAI treatment, tyrosine-kinase inhibitors, surgery, EBRT, and MIT [26]. MIT is proposed in the multidisciplinary approach to patients

with RAI refractory metastatic thyroid cancer who are fragile or not amenable to surgery. The aim being local disease control in oligometastatic or oligoprogressive patients and/or pain palliation with minimal invasion. However, outcome evidence is limited and of modest quality.

Recommendation 16. Consider TA for the palliative treatment of painful bone metastases. Ablation may be proposed alone or in combination with bone consolidation and EBRT to improve the clinical outcome (1, ØØOO).

Recommendation 17. Consider TA, alone or in combination with EBRT, with a local curative intent for <20 mm bone metastases (2, ØOOO).

Bone metastases from thyroid cancer most frequently affect the spine, causing significant deterioration in quality of life, often leading to neurological symptoms and pathological fractures. Besides repeated RAI therapy in cases with radioiodine uptake, treatment options include surgical resection, vertebroplasty, EBRT, and MITT. A prospective multicenter study [131] showed that RFA provided substantial pain relief from bone metastases at the 3-month follow-up. Similarly, a cryoablation study [132] found that pain scores dropped from 7.1/10 before treatment to 5.1/10 at 1 week and 1.4/10 at 24 weeks, with 83% of patients reducing their opioid use posttreatment. LA was also used for six DTC bone metastases resistant to high-dose RAI, combined with EBRT and opioids [133].

The most common complication following bone ablation procedures is secondary fractures [133, 134]. For this reason, TA should be paired with bone reinforcement techniques, such as osteoplasty or osteosynthesis, especially in weight-bearing bones [135].

Recommendation 18. Consider TA for residual RAI-refractory oligo-metastatic lung (sized <2 cm) and liver (sized <3 cm) DTC metastases, preferentially in the context of a multimodality approach (1, ØOOO).

A study involving the RFA treatment of 1037 lung metastases from various primary cancers, including colon, rectum, kidney, and thyroid (the latter making up only 3%), demonstrated promising outcomes with up to four treatments without major complications. Progression-free survival and local tumor progression rates were 40.2% and 13.1% at 1 year, and 5.9% and 11.0% at 4 years, respectively [136]. Factors linked to poorer survival included primary cancers other than colon or kidney, a disease-free interval of ≤1 year, tumor size >20 mm, and the presence of more than two pulmonary metastases.

Experience with TA in the treatment of liver metastases, particularly from various cancers, is extensive [130, 137], though specific data on thyroid cancer metastases to the liver are limited. Case reports involving LA and RFA have shown these methods to be effective in reducing tumor burden quickly, with notable, though temporary, symptom relief [138, 139]. Therefore, TA should be considered as part of a multimodal strategy for DTC patients at surgical risk or when other treatments fail.

4 Questions for Self-Assessment

1. Which of the following is a key advantage of minimally invasive treatments for benign thyroid nodules over traditional surgery?

   (a) Higher recurrence rate
   (b) Increased hospital stay
   (c) Less cosmetic impact and reduced complications
   (d) Mandatory general anesthesia

   Correct answer: (c) Less cosmetic impact and reduced complications
2. According to the European guidelines, which of the following is the *first-line* treatment for a purely cystic thyroid nodule?

   (a) Radiofrequency ablation
   (b) Microwave ablation
   (c) Laser ablation
   (d) Ethanol ablation

   Correct answer: (d) Ethanol ablation
3. Which of the following MITs is most commonly used for solid, nonfunctioning benign thyroid nodules?

   (a) Ethanol ablation
   (b) Radiofrequency ablation
   (c) Fine-needle aspiration
   (d) Levothyroxine suppression therapy
   Correct answer: (b) Radiofrequency ablation

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Diabetic Osteoporosis: Clinical Case

Maria Grazia Radaelli and Francesco Di Marco

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Chapter Introduction: What You Will Learn in This Chapter
In this chapter, we will focus on the intersection of diabetes and osteoporosis, two prevalent conditions that significantly affect patient health. Diabetes, both type 1 and type 2, is increasingly recognized as a risk factor for osteoporosis, a condition characterized by low bone mass and increased fracture risk. Through the exploration of clinical cases, we will examine the mechanisms by which diabetes influences bone metabolism, the increased risk of fractures in these patients, and the impact of antidiabetic treatments on bone health. We will also discuss diagnostic approaches and treatment strategies to address osteoporosis in diabetic patients.

Key Points
- The relationship between diabetes (both type 1 and type 2) and osteoporosis.
- Pathophysiological mechanisms linking diabetes with bone loss and fracture risk.
- The role of antidiabetic medications in influencing bone metabolism.
- Clinical approaches for diagnosing and managing osteoporosis in diabetic patients.

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Learning Objectives
By the end of this chapter, you will be able to:

- Understand the mechanisms linking diabetes to osteoporosis.
- Recognize the increased fracture risk in patients with diabetes and the contributing factors.
- Analyze the impact of different antidiabetic therapies on bone health.
- Apply clinical strategies for diagnosing and managing osteoporosis in patients with diabetes.

Definitions
Before diving into the main content, here are some key terms to familiarize yourself with:

- *Osteoporosis*: A condition characterized by weakened bones, increasing the risk of fractures. It is defined by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue.
- *Diabetes Mellitus*: A metabolic disorder marked by high blood glucose levels due to either insufficient insulin production (type 1 diabetes) or insulin resistance (type 2 diabetes).
- *Fracture Risk*: The likelihood of a patient experiencing a bone fracture, which can be influenced by osteoporosis, comorbidities (like diabetes), and medications.
- *Bone Metabolism*: The dynamic process involving the breakdown of bone tissue (resorption) and its formation (osteogenesis), regulated by various factors including hormones, nutrition, and physical activity.
- *Antidiabetic Medications*: Drugs used to manage blood glucose levels in diabetic patients. Some medications, like glucagon-like peptide-1 agonists (GLP-1) and sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors), may have effects on bone metabolism.

1 Background

The idea that diabetes targets bone and that bone fragility is a consequence of this illness is being supported by an increasing amount of evidence. Nowadays the term "diabetic osteoporosis" is commonly used to describe alterations in bone density and remodeling caused by diabetes mellitus (type 1 or type 2).

Patients affected by T1DM (Type 1 Diabetes Mellitus) have a higher overall fracture risk than those with T2DM (Type 2 Diabetes Mellitus); specifically, their relative risk for any fracture is 1.51, while for femoral fracture it is 4.35 [1]. Hip fractures typically occur 10–15 years before nondiabetic individuals, and the risk is elevated in both male and female patients with T1DM at all ages [2]. T1DM patients also have a higher prevalence of vertebral fractures (24.4 vs. 6.1%) respect to control [3]. Although T2DM patients often have an increased bone mineral density (BMD) than controls [4, 5], they have a much higher incidence of fracture [6] most

likely a result of lower bone total resistance. This decreased resistance is a result of poor bone quality, which is also brought on by changes in the microarchitecture, strength, composition, and remodeling of the mineral and bone matrix [7]. The increased risk of fractures is explained by microarchitecture deterioration, since "Diabetic osteoporosis" is a "low-turnover" osteoporosis [8], that is the presence of a reduced bone ability to repair from microcracks (bone remodeling) and this explains why T2DM patients have low values of bone alkaline phosphatase (bALP), osteocalcin, and C-terminal telopeptide of type I collagen; (CTX). Studies also show that the WNT/B-catenin pathway is inhibited when bALP, CTX, and B-catenin levels are decreased, while sclerostin and Dkk1, two proteins that regulate osteoblastic activity, are increased [9]. Other factors that contribute to enhanced bone fragility are first of all the low-grade chronic inflammation, which is the fundament for different metabolic diseases such as diabetes either type 1 and type 2 [10–12] but also the increased adipogenesis of adipose tissue located at the bone marrow [13]. Finally, elevated glycemia increases calcium urinary excretion and parathyroid hormone (PTH) levels [14–16] with a consequent alteration of calcium-phosphate metabolism, with an explained role in the pathogenesis of bone fragility. Generally, a good glycemic control contributes to a better bone health, and a long-lasting disease is associated to a higher fracture risk [17], either in T1DM [18] or T2DM. Another aspect to consider is the ongoing therapy. In patients with type 2 diabetes, the usage of some hypoglycemic drugs is associated with a higher risk of fracture, and also polytherapy, which increases with age, is another important risk factor for the falls [19]. In patients with T2DM, therapy such as thiazolidinediones, sulfonylureas, and SGLT2-inhibitors should be used with caution, canagliflozin in particular. Drugs with a neutral or favorable impact on bone metabolism [i.e., metformin or incretins (GLP1-RA or DPPIV-inhibitors)] should be preferred. Here we present a case of a woman affected by T2DM with typical features of "diabetic osteoporosis" as we can see in the following.

2 Clinical Case

Our patient is a 60-year-old woman who was referred to our Center for a control in T2DM known from 2010, treated first with metformin and pioglitazone for 10 years, and then with dulaglutide 1.5 mg 1 injection/a week. Her past medical history included dyslipidemia in therapy with rosuvastatin/ezetimibe 5/10 mg, essential hypertension in therapy with losartan 50 mg, amlodipine 5 mg. She had also osteopenia in therapy with cholecalciferol 25,000 UI every 15 days. Her family medical history was positive for T2DM and osteoporotic fracture (her mother had a previous femoral fracture). Menopause at 50 years, no HRT, one pregnancy with no complications. She smokes 12 cigarettes a day, doesn't consume alcol. Her blood exams showed: glycemia 95 mg/dL, HbA1c 56 mmol/mol, creatinine 0.63 mg/dL, eGFR 95 mL/min, total cholesterol 162 mg/dL, HDL 61 mg/dL, triglycerides 140 mg/dL, LDL 73 mg/dL, hepatic function on target, normal microalbuminuria; previous

exams showed a chronic HbA1c >55 mmol/mol. Glycemia was always between 120 mg and 160 mg/dL. No complications for T2DM (no diabetic retinopathy, sinus rhythm). Echocardiogram showed an ejection fraction (EF) >50% with no other kinetic alterations; the carotid doppler showed no stenosis. We suggested the patient to perform other specific blood exams, which showed 25O hvitD 41.7 ng/mL, PTH 47.4 pg/mL, phosphorus 4.2 mg/dL, corrected calcium 9.1, ALP 41 U/L, creatinine 0.68 mg/dL, TSHr 2.1, CTX 0.557 ng/mL, normal electrophoresis, and normal calciuria. The X-ray-absorptiometry confirmed her osteopenia with a lumbar (L1-L4) T score of −2.3, a femoral neck T-score of −1.4, and a total femoral T-score of −1.5; the lumbar and dorsal spine X-ray showed a non-dateable L2 fracture in the absence of specific trauma.

3 Discussion

This patient has several characteristics, which help us to explain what we call "diabetic osteoporosis." In fact, she has multiple risk factors for developing osteoporosis in relation to the presence of T2DM. First of all, she has a long-lasting T2DM (10 years), which is a known risk factor, mainly because chronic hyperglycemia and consequent formations of advanced age product of glycosylation [20–22]. Moreover, her glycemic control wasn't at target, in fact also her blood exams of previous years showed a HbA1c never below 52 mmol/mol. An inadequate glycemic control, especially for years, is linked to a major risk of developing complications such as diabetic osteoporosis.

Another feature typical of diabetic osteoporosis and well represented in our patient is her BMD within the range of osteopenia, even though she had a lumbar L2 fragility fracture, highly suspicious for alterations in her bone microarchitecture. In fact, although it has been demonstrated that BMD underestimate the fracture risk in T1DM and in T2DM, the BMD reduction remains still an independent fracture risk [23]. It is important to delineate that with the same T-score and the same age, the fracture risk is higher in T2DM patients than nondiabetic controls. Particularly, a T-score in a woman with T2DM is equivalent to a fracture risk of a nondiabetic woman with a 0.5 units lower T-score [24], accounting for a lumbar (L1-L4) T score of −2.8, and a total femoral T-score of −2.0 in our patient. In addition, antidiabetic treatments in our patient could have contributed to her ongoing bone pathology. In particular, she was treated for years with glitazones, which are known to be associated with a higher fracture risk especially after many years of treatment: Through peroxisome proliferatoractivated Receptor gamma (PPARy) activation, they stimulate adipogenesis in bone tissue and suppress osteoblastogenesis with a consequent reduction on BMD. Treatment with GLP1-RA instead has not been associated with a higher fracture risk.

In our patient, we evaluated FRAX risk fracture assessment, which resulted in 20% of main osteoporotic fractures and 4.8% of hip fractures; thus we decided to begin a therapy with bisphosphonate associated with supplementation with cholecalciferol and indications for a diet rich in calcium. In order to prevent the complications linked to the "diabetic osteoporosis" of our patient, we began to assess

periodically also her bone metabolism and bone status evaluating vertebral and femoral densitometry and blood, urines, and bone health–related exams, in particular calcium, phosphate, albumin, PTH, 25-OH-vitamin-D, creatinine, alkaline phosphatase, and c-terminal telopeptide.

Finally We decide to change her diabetic therapy, stopping pioglitazone and starting dulaglutide to obtain a better glycemic control an also a lower fracture risk.

4 Conclusions

Bone should be included among tissues affected by diabetes, thus considering bone fragility as a possible complication of diabetes. In these patients we should have a more intense care, taking into account their higher fracture risk, performing DEXA, FRAX, or Derived Fracture Risk Assessment (DeFRA), and eventually TBS for a more specific idea of their bone structure/microarchitecture. Also, in those with a good glycemic control, we should pay attention to the therapy, preferring drugs with a neutral effect on BMD. We can also eventually consider adding anti-osteoporotic drugs: not only bisphosphonate or denosumab, but also anabolic ones. Drugs such as Teriparatide or Romosozumab could be the appropriate choice in some patients, considering also the nature of diabetic osteoporosis, which is a low-turnover osteoporosis.

Questions for Self-Assessment
Test your understanding with the following questions:

1 *What is the primary link between diabetes and osteoporosis?*

(a) Insulin resistance leading to bone formation
(b) Hyperglycemia inducing bone resorption
(c) Elevated calcium levels improving bone density
(d) Low blood glucose levels protecting bone health

Correct answer: (b) Hyperglycemia inducing bone resorption

2 *Which antidiabetic medication is known to have an impact on bone metabolism?*

(a) Metformin
(b) GLP-1 receptor agonists
(c) SGLT2 inhibitors
(d) Insulin

Correct answer: (c) SGLT2 inhibitors

3 *Why are diabetic patients at an increased risk for fractures?*

(a) Due to decreased calcium absorption in the gut
(b) Because of impaired bone formation and increased resorption
(c) Due to elevated parathyroid hormone (PTH) levels
(d) Because they have higher bone mineral density

Correct answer: (b) Because of impaired bone formation and increased resorption

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